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Anesthesia and Analgesia

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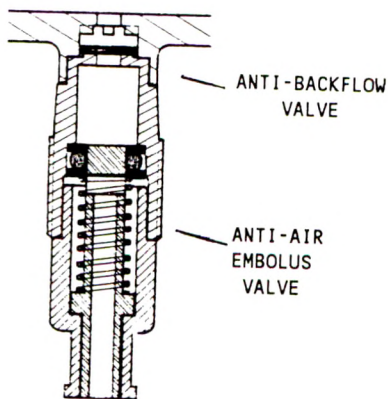
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Editorials

Does 1 + 1 = 2?

Edmond I. Eger, MD

Key Words: POTENCY, ANESTHETIC: enflurane—nitrous oxide. ANESTHETICS, VOLATILE: enflurane. ANESTHETICS, GASES, nitrous oxide. INTERACTIONS (DRUG), ENFLURANE—nitrous oxide.

The "unitary theory of narcosis" asserts that all anesthetics act in the same way, a characteristic attractive to those of simple mind (e.g., this editorialist) who prefer simplicity to complexity, order to chaos. The unitary theory requires an identity of action at a molecular level. One test of its validity is additivity: Is the sum of the effect of two anesthetics given concurrently the same as the effect of the individual anesthetics? For example, does half MAC of one agent plus a half MAC of another agent produce the same effect as one MAC of either agent? If it does, then the unitary theory is supported. If it does not, if for example, three-quarters of a MAC of one agent must be added to three-quarters of another to produce the same effect as one MAC of either, then the unitary theory is compromised.

The data reported by Cole, Kalichman, and Shapiro ("The Nonlinear Contribution of Nitrous Oxide (N_2O) at Sub-MAC Concentrations to Enflurane MAC in Rats") in this issue of the Journal have been interpreted to indicate a nonadditive effect of the combination of N_2O and enflurane (1). The basis for their argument may be seen in Figure 2 of that article. Regression analysis for the enflurane MAC values associated with the three smallest concentrations of N_2O (0%, 10%, and 30%) produces a line that lies under all enflurane MAC values for the remaining three concentrations (60%, 70%, and 80%). Furthermore, the line intercepts the abscissa at 150% (of an atmosphere) N_2O, a partial pressure that might be

predicted to be the MAC of N_2O in rats. The prediction that MAC is 150% is based, in part, on the "predictable" ratio of MAC in rats to MAC in humans (2). The prediction also is supported by the results from the study by Di Fazio et al., who obtained an estimate of 136% N_2O (3).

I prefer, however, an alternative interpretation that diametrically differs from that provided by Cole, Kalichman, and Shapiro: I would argue that the data *do* support the notion that the effects of inhaled anesthetics are additive. There are three parts to my argument.

First, Cole, Kalichman, and Shapiro arbitrarily selected the smallest three values of N_2O and the associated enflurane MAC values for their regression analysis. They obtained a very good correlation for this relationship and noted that the points for the greater N_2O values lie above the line defined by this correlation. I also have made this calculation for the average values for the three smallest (N_2O) pairs from their Table 2 and find an R^2 (adjusted) of 97.9%. However, this correlation is no better than the correlation for the five pairs that exclude the value for 30% N_2O. The R^2 (adjusted) for the five pairs is 98.6%. My inclination would be to accept more than fewer data in any analysis, particularly when the correlation is not impaired by such acceptance! It would seem likely to me that "outliers" are in the values for 30% N_2O rather than in the values for 60%, 70%, *and* 80%. Given the smallness of the changes in enflurane MAC (the maximum change [32% of the MAC without N_2O] was produced by 80% N_2O) and given that some variability exists in MAC (6.5% of the MAC value for the data in the Cole study), it is not surprising that one of six values with N_2O differed a bit from the prediction given by regression through the other values. Furthermore, the focus by Cole et al. on the 10% and 30% points may be unfortunate, because such data are usually more variable and

uncertain than data extended further out on a dose-response curve.

Second, no one has determined the MAC for N_2O for rats. The argument that 150% is a reasonable value may be valid, but the argument is based on extrapolations from two studies, not on actual determinations. Extrapolations from data produced in other studies give higher values. For monkeys a value of 200% was obtained (4); for cats the value was 255% (4). More important, the data from the study by Wolfson et al. in rats (the animals used by Cole et al.) give an extrapolated value of 217% for the MAC of N_2O (5). MAC has been directly determined in two species: the dog (190%) (6) and mouse (275%) (7). These results suggest that a MAC value considerably greater than 150% would not be unreasonable. Extrapolation of the line defined by the regression for the data given by Cole, Kalichman, and Shapiro for all pairs *except the pair associated with 30% N_2O* gives a MAC of 239%.

Third, data do exist for the additivity of N_2O and enflurane in humans (8). These data include data for MAC for N_2O (9) alone and enflurane alone (10). The results show simple additivity. One might ask why rats should differ in this respect from humans.

However interesting, the data presented by Cole, Kalichman, and Shapiro do not necessarily document a nonadditive effect for inhaled anesthetics. Such documentation would require a direct determination of the MAC of N_2O, not a determination by extrapolation. Absent such a determination, I shall continue to believe that $1 + 1 = 2$.

References

1. Cole DJ, Kalichman MW, Shapiro HM. The nonlinear contribution of nitrous oxide at sub-MAC concentrations to enflurane MAC in rats. Anesth Analg 1989;68:553–9.

2. Drummond JC. MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: and a test for validity of MAC determinations. Anesthesiology 1985;62:336–8.

3. Di Fazio CA, Brown RE, Ball CG, Heckel CG, Kennedy SS. Additive effects of anesthetics and theories of anesthesia. Anesthesiology 1972;36:57–63.

4. Steffey EP, Gillespie JR, Berry JD, Eger EI II, Munson ES. Anesthetic potency (MAC) of nitrous oxide in the dog, cat and stump-tailed monkey. J Appl Physiol 1974;36:530–2.

5. Wolfson B, Hetrick WD, Lake CL, Siker ES. Anesthetic indices—further data. Anesthesiology 1978;48:187–90.

6. Eger EI II, Brandstater B, Saidman LJ, Regan MJ, Severinghaus JW, Munson ES. Equipotent alveolar concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon and nitrous oxide in the dog. Anesthesiology 1965;26:771–7.

7. Deady JE, Koblin DD, Eger EI II, Heavner JE, D'Aoust B. Anesthetic potencies and the unitary theory of narcosis. Anesth Analg 1981;60:380–4.

8. Torri G, Damia G, Fabiani ML. Effect of nitrous oxide on the anaesthetic requirement of enflurane. Br J Anaesth 1974;46:468–72.

9. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man. Anesth Analg 1982;61:553–6.

10. Gion H, Saidman LJ. The minimum alveolar concentration of enflurane in man. Anesthesiology 1971;35:361–4.

The Long and the Short of Conduction Block

B. Raymond Fink, MD

Key Words: ANESTHETICS, LOCAL: lidocaine, mode of action. NERVE, AXONAL BLOCKADE.

Progress in the science of anesthesiology increasingly depends on the efforts of scientists trained in the fundamental medical sciences. Nowhere is this progress more evident than in neuropharmacology, the bedrock of the specialty. The article in this issue by Raymond et al. (1) is a very good example; it is provocative with new information and corrective of some old.

The first lesson demonstrated by Raymond and coworkers (1) concerns the minimum length of nerve fiber that needs to be exposed to anesthetic when one is to achieve conduction block. They show in one myelinated axon at a time that in low concentrations of anesthetic this length bears an inverse relation to the concentration, a relation that agrees with what Fink and Cairns (2) had deduced from other research. Raymond et al. (1), however, rightly point out that Fink and Cairns' interpretation was marred by a confusing semantic error that blunted the impact of their data and conclusion. The contribution by Raymond et al. (1) goes far beyond mere confirmation; it introduces important original information on the limits of the relation and in the process brings to general attention the long forgotten phenomenon of block by decremental conduction.

Decremental conduction has been investigated and neglected more than once. As first described in 1881 by Szpilman and Luchsinger (cited in Reference 3), it occurred in a partially narcotized length of nerve and attracted much interest because it seemed to contravene the norm of "all-or-none" impulse conduction. We now know that in the partially anesthetized region the active response at one node of Ranvier initiates at the next node only an impulse of smaller magnitude. Consequently, the impulse and the speed of conduction progressively decrease during propagation and may eventually be extinguished. After the "all-or-none" character of conduction in normal axons was proved, arguments about decremental conduction subsided until Lorente de Nó and Condouris (3) proved its presence in the compound action potential (CAP) of myelinated A-fibers exposed to 2 and 4 mM procaine. This evidence did not receive recognition in textbooks (4,5), however, perhaps because decremental conduction resists direct experimental demonstration in individual axons; it is as yet technically impractical to measure the current at a succession of nodes in one and the same fiber. But Condouris et al. (6) have modeled it mathematically in frog myelinated axon with the aid of a computer using Hodgkin and Huxley's equations suitably modified for frog nodes of Ranvier. Simulation of the effect of tetrodotoxin (TTX) demonstrated that a 74% depression of sodium conductance yields an impulse that decrements in amplitude at successive nodes until conduction is extinguished (Figure 1); the simulation for lidocaine, a drug that produces combined depression both of sodium and potassium conductances, yielded a more gradually decrementing conduction. However, there is little potassium conductance at mammalian nodes (7) so the TTX simulation is perhaps more germane to the effect of lidocaine on mammalian axons than the Condouris (6) simulation of the action of lidocaine.

Decremental conduction was overlooked in anesthesiology until a benchmark review by Raymond and Gissen (8) drew attention to its impact on the length of axon needing exposure to anesthetic and to the lack of experimental data on the subject. Anesthesiological understanding has previously relied on Tasaki's (9) finding that with a high concentration of local anesthetic, three consecutive nodes must be inactivated to block conduction completely. Franz and Perry (10) applied this principle to explain differential block as a function of time and diffusion, the internodal distances being much greater in large than in small diameter myelinated axons. Raymond et al. (11) now present the first measurements on critical
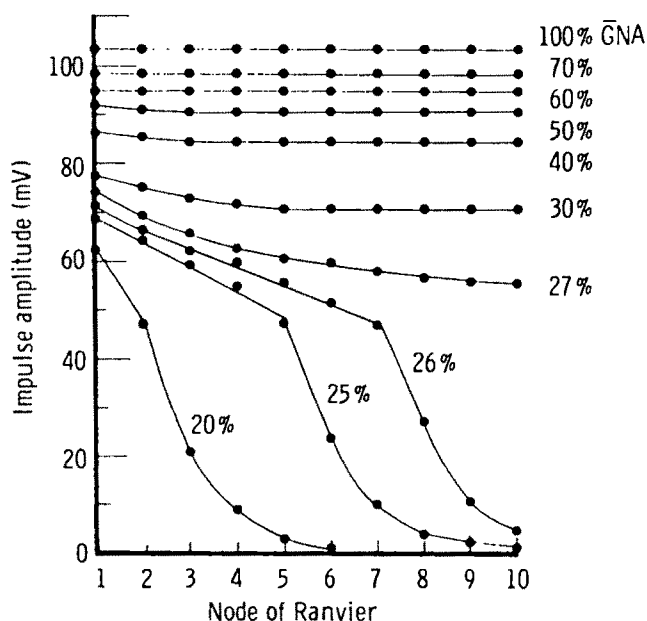
Figure 1. Computer representation of decremental conduction from Condouris et al. (6). The effect of tetrodotoxin (TTX) on conduction characteristics of a mathematical model of myelinated axon was simulated by varying the sodium conductance ($\bar{g}_{Na}$). The model originally comprised 13 nodes of Ranvier at 2-mm intervals. Each point on the curves represents the peak of an action potential rising from the baseline. The magnitude of the residual $\bar{g}_{Na}$ is indicated beside each curve. Decrease of $\bar{g}_{Na}$ to 60% of normal, equivalent to very weak local anesthetic, produced a small initial decrement of the impulse followed by uniform propagation through the remaining "anesthetized" nodes. With greater decreases of $\bar{g}_{Na}$ to 30% of normal, the decremental process continued through an increasing number of nodes and with decrease to 27% involved 10 nodes. The greatest decreases, to 26, 25, and 20% of normal, produced initially linear decrements that abruptly gave way to an exponential decline to baseline signifying block of conduction; the rate constant of the decline was the same for all three. (Reproduced by permission from J Pharmacol Exp Ther 1976;196:740.)

length at several low concentrations of lidocaine hydrochloride for individual frog A-fibers as well as for whole nerve CAPs. The measurements are not profuse because the technique is extremely arduous and exacting. The shortest measured critical lengths were 6–7 mm, and at these lengths the critical blocking concentration of lidocaine varied between 1.2 and 1.5 mmol/L. At the longest critical lengths measured, 22–28 mm, the critical concentrations were 0.6–0.3 mmol/L lower and ranged from 0.6–1.3 mmol/liter. These lengths fall within the range of anesthetic-bathed lengths of rabbit myelinated axons studied by Fink and Cairns (2), where the lidocaine ED_{50} for a 15-mm length of bathed nerve fiber was 0.6 mmol/L. The interpolated critical blocking concentration at this length in the Raymond et al. (11) study ranged from 0.7–1.4 mmol/L and averaged nearly 1.2 mmol/L. This average suggests that the critical concentration in amphibian axons at 17°C was about twice as great as

that in mammalian axons at 37°C; neither series showed any correlation between blocking concentration and axonal size (as inferred from conduction velocity).

The news from Raymond et al. (11) is comforting for anesthesiologists because it implies that a 1% lidocaine hydrochloride solution (approximately 36 mmol/L) at the nerve fibers provides a large excess even at short infiltrated length, and that use of a weaker solution in the interest of safety can be compensated for up to a point by infiltrating a correspondingly greater length of nerve, although probably at the price of a shorter effective duration of block.

The second new and highly original feature in Raymond et al. (11) is the application of decremental conduction to explain the observed critical relation between exposed length of axon—the "limit length" as defined by Lorente de Nó and Condouris (3)—and local anesthetic concentration. In their view, the new evidence excludes the hypothesis presented by Fink and Cairns (2) that had hewed to the three node block interpretation. The latter hypothesis proposed that when bathed by a near ED_{50} concentration of local anesthetic, a length of nerve greater than the minimal three-node length will have to be exposed to the drug to assure block because the susceptibility to block may be assumed to differ somewhat from node to node. This hypothesis still seems tenable as an alternative or complement to block by decremental conduction. After the preliminary report by Raymond et al. (11), both hypotheses were applied to elucidate the segmental differential blocks encountered during axial blockade (12).

Raymond et al. (11) give several reasons for rejecting the Fink and Cairns (2) hypothesis without qualification. However, the uncertainties of the new observations—and hypothesis—should not be underrated. The choice of hypotheses depends in part on the degree of variability of sensitivity to anesthetic from node to node in any one fiber. Raymond et al. (11) assume it to be negligible. However, the firing threshold of successive nodes has shown a nonuniform variation of 50% over a 12-mm length of fiber containing eight nodes (13); in such an experiment, variability could have been due in part to a cause other than the change in relative positions of the nodes and electrode; that is, it could have been due to real differences in excitability. Short of measurements of the factor of safety in a series of consecutive nodes, which do not yet exist, the question presumably remains unanswered. Again, in support of axonal homogeneity, both of conduction safety and of susceptibility to anesthetic, Raymond et al. (11) comment that they always observed "slight" increases in criti-

cal length with "slight" decreases in lidocaine concentration and larger increases in critical length with larger decreases in concentration (1). However, this result is not what the curves in Figure 6 of their article suggest. In that figure, one sees several relatively large increases in critical length with "slight" decreases in lidocaine concentration and one or more smaller increases in critical length with a relatively large increase in lidocaine concentration, tending to negate the proposed homogeneities.

How well do the lidocaine data in the study agree with the Condouris (6) computed forecasts of decremental conduction block? Unfortunately, a comparison is not possible because the published computed curves are available only for TTX. An experimental study of TTX in the Raymond (11) system will be of considerable interest.

In brief, at this time the arguments for choosing between the two rival hypotheses or "images" do not appear compelling, and one may be safer in provisionally regarding them as mutually nonexclusive.

In writing about the value of CAP depression as a measure of the incidence of conduction block, Raymond et al. (11) estimate that on the average their CAPs erred by 20%, confirming the well known fact that CAPs as a measure of block are not very reliable. Incidentally, their average value was the mean of three values, one of which amounted to 50%, or more than the supposed overestimate by Fink and Cairns (2). The perils of CAPs are illustrated by a rash remark in the work of Lorente de Nó and Condouris (3). Finding that decremental conduction of CAPs was caused by anesthetics as well as by decrease of sodium ions or increase in potassium ions, they commented: "Consequently it is impossible to accept any hypothesis, such as the Hodgkin-Huxley hypothesis, in which the magnitude of the nerve impulse is supposed to be directly determined by the concentration of sodium and potassium ions outside the nerve fibers."

All of this in no way diminishes the importance of the latest study by Raymond and coworkers (11). It casts new light on the role in regional blockade of the length of nerve exposed to anesthetic. It places in limbo present ideas about C_m, the minimal concentration of local anesthetic necessary to block conduction. C_m will henceforth have to be defined for a

standard length of axon. As mentioned by Raymond et al. (11), their results do not exclude the possibility of producing a strongly differential block of pain by restricting the exposure length. This possibility is a very interesting point because the body may be doing just that when epidural blockade is performed with a low concentration of local anesthetic (12). We are surely destined to hear much more about decremental conduction block—as well as three-node block—now that Raymond and coworkers have persuasively brought the concept of conduction with decrement to the attention of anesthesiologists.

References

1. Raymond SA, Steffensen SC, Gugino LD, Strichartz GR. The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg 1989;68:563–70.

2. Fink BR, Cairns AM. Lack of size-related differential sensitivity to equilibrium conduction block among mammalian myelinated axons exposed to lidocaine. Anesth Analg 1987:948–53.

3. Lorente de Nó R, Condouris G. Decremental conduction in peripheral nerve. Integration of stimuli in the neuron. Proc Natl Acad Sci USA 1959;45:502–617.

4. Katz B. Nerve, Muscle, and Synapse. New York: McGraw-Hill, 1966:95.

5. Brinley FJ Jr. Excitation and conduction in nerve. In: Medical Physiology, 17th ed. Mountcastle VB, ed. St. Louis: CV Mosby, 1980:45–81.

6. Condouris GA, Goebel RH, Brady T. Computer simulation of local anesthetic effects using a mathematical model of myelinated nerve. J Pharmacol Exp Ther 1976;196:737–45.

7. Chiu SY, Ritchie JM. On the physiological role of internodal potassium channels and the security of conduction in myelinated nerve fibers. Proc R Soc Lond (Biol) 1984;220:415–22.

8. Raymond SA, Gissen AJ. Mechanisms of differential block. In: Strichartz GR, ed. Handbook of Experimental Pharmacology, Vol. 81: Local Anesthetics. Berlin: Springer-Verlag, 1987:95–164.

9. Tasaki I. Nervous Transmission. Springfield: Thomas, 1953: 164.

10. Franz DN, Perry RS. Mechanism for differential block among single myelinated and non-myelinated axons by procaine. J Physiol (Lond) 1974;236:193–210.

11. Raymond SA, Steffensen SC, Gugino LD, Strichartz GR. Critical exposure length for nerve block of myelinated fibers with lidocaine exceeds three nodes. Reg Anaesth 1988;12:S46.

12. Fink BR. Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. Anesthesiology 1989;70;(in press).

13. Carley LR, Raymond SA. Comparison of the after-effects of impulse conduction on threshold at nodes of Ranvier along single frog sciatic axons. J Physiol (Lond) 1987;386:503–7.

The Nonlinear Contribution of Nitrous Oxide at Sub-MAC Concentrations to Enflurane MAC in Rats

Daniel J. Cole, MD,* Michael W. Kalichman, PhD, and Harvey M. Shapiro, MD

COLE DJ, KALICHMAN MW, SHAPIRO HM. The nonlinear contribution of nitrous oxide at sub-MAC concentrations to enflurane MAC in rats. Anesth Analg 1989;68:556–62.

The presumed linear relationship describing the contribution of nitrous oxide (N_2O) to the enflurane requirement necessary to achieve a 1.0 MAC level of anesthesia was tested in rats ($N = 84$). Each rat received one of six different concentrations of N_2O, and enflurane was adjusted to attain 1.0 MAC with the use of a standard tail clamp method. The resultant group MAC anesthetic concentrations were Group I-N_2O = 0.0%, enflurane = 2.30%; Group II-N_2O = 10.4%, enflurane = 2.19%; Group III-N_2O = 30.7%, enflurane = 1.85%; Group IV-N_2O = 61.8%, enflurane = 1.75%; Group V-N_2O = 70.9%, enflurane = 1.56%; and Group VI-N_2O = 80.3%, enflurane = 1.54%. Increasing the N_2O concentration from 0–10%, from 30–60%, or 70–80% did not significantly decrease the enflurane requirement; however, increasing the N_2O concentration from 10–30% or 60–70% produced a significant decrease ($P < 0.05$) in the concentration of enflurane required for 1.0 MAC of anesthesia. Thus, in rats, increasing the concentration of N_2O in sub-MAC ranges did not produce a linear decrease in the enflurane concentration required to add up to 1.0 MAC of anesthesia. These results are consistent with a dose-dependent interaction between N_2O and the excitatory properties of enflurane; this interaction could represent synergism at low concentrations or antagonism at higher concentration of N_2O.

Key Words: POTENCY, ANESTHETIC: enflurane—nitrous oxide. ANESTHETICS, VOLATILE: enflurane. ANESTHETICS, GASES, nitrous oxide. INTERACTIONS (DRUG), ENFLURANE—nitrous oxide.

MAC, a measure of inhalational anesthetic potency, was originally defined as the "minimum alveolar concentration necessary to prevent purposeful movement in response to a painful stimulus" (1,2). Because effective concentrations vary among individuals, clinical evaluations of MAC are made by determining the concentration at which 50% of the individuals tested would not respond to a painful stimulus. The first MAC determinations were performed with single volatile anesthetic agents. Shortly after the original MAC studies, it was found that the addition of 70% nitrous oxide (N_2O) reduced the halothane anesthetic requirement by 61% (3). Thus, the concept of additive MAC was introduced.

The clinical consensus among anesthesiologists is that in humans, MAC for a volatile anesthetic linearly decreases by about 1% for each 1% of N_2O added to the inspiratory gases. This concept is supported by previous studies in which only one or two concentrations of N_2O were tested in a given study (3–7). Few studies have specifically evaluated this assumed linear relationship between multiple concentrations of N_2O and the dose of an inhalational agent required to obtain 1.0 MAC of anesthesia (8–10). In studies where multiple concentrations of N_2O were tested, the results have not led to a consistent definition regarding the contribution of N_2O to MAC (8–10). In one study, Difazio et al. (8) observed that the combination of N_2O and cyclopropane produced less of an effect than the sum of the individual anesthetic properties, suggesting a nonlinear antagonistic effect. We were unable to find any data on additive anesthetic properties when N_2O and enflurane were used in more than two combinations within a given study. In the present study, we determined the effect of six different N_2O concentrations on the enflurane requirement to achieve MAC.

Methods

With prior approval by the Institutional Animal Studies Subcommittee, male Sprague-Dawley rats (N = 84) of similar ages and weights were separated into six equal groups corresponding to administered N_2O concentrations of 0, 10, 30, 60, 70, and 80%.

All studies were performed between 7:00 a.m. and 3:00 p.m. Anesthesia was induced in a 2.5 liter plexiglass box with a fresh gas flow of 1.5 liter/minute consisting of a 50:50 ratio of oxygen and N_2O and 3.0% enflurane. Each rat was then orotracheally intubated with use of the otoscope method and was mechanically ventilated with a Harvard Rodent ventilator at a frequency of 60 breaths/minute and a tidal volume of 10 ml/kg of body weight. After tracheal intubation, each rat was assigned one of the following anesthetic regimens: Group I-N_2O = 0%, enflurane = 2.4%; Group II-N_2O = 10%, enflurane = 2.3%; Group III-N_2O = 30%, enflurane = 2.0%; Group IV-N_2O = 60%, enflurane = 1.8%; Group V-N_2O = 70%, enflurane = 1.7%; and Group VI-N_2O = 80%, enflurane = 1.7%. The initial enflurane concentration was based on pilot studies and was designed to be slightly above a predicted MAC. The N_2O concentrations were also based on pilot studies and were designed to fall on that portion of the N_2O dose-response curve with maximal slope. In groups I–IV the inspired oxygen concentration was 40%, whereas in groups V and VI, the inspired oxygen concentration was 30 and 20%, respectively. With the aid of a surgical microscope, a femoral arterial catheter was placed in each animal for continuous blood pressure monitoring. In preliminary studies, rats allowed to recover after placement of a femoral arterial catheter had good function of all limbs. The total preparation period was approximately 45 minutes after which at least 75 minutes elapsed during which the rat was not disturbed. The total anesthetic stabilization period was at least 120 minutes in all rats. Arterial blood gases were analyzed on a Radiometer[R] blood gas analyzer using microsample technique (<100 μl). Hematocrit was determined by a DAMON/IEC[R] micro hematocrit centrifuge and capillary reader, with use of microsample technique (25 μl). Temperature was monitored rectally (Yellow Springs Instruments[R]) and servo-controlled at 37°C with a heating pad. The ventilation system consisted of an endotracheal tube made of PE-240 tubing (approximately 14-gauge) attached to inspiratory and expiratory circuits via a three way Y-connector. A rubber plug with a leak free orifice was permanently placed at the central port of the three way Y-connector. Sampling of end-tidal gases (enflurane, N_2O, and carbon dioxide) was achieved by passing a lubricated 20-gauge blunt needle through the plugged orifice of the central port to the distal tip of the endotracheal tube. Gases were analyzed on-line by a Perkin-Elmer mass spectrometer with a sampling rate of 60 ml/minute. During sampling of end-tidal gases, the respiratory frequency was decreased to 40 breaths/minute and the tidal volume was increased by 33%. This technique provided optimal sampling of end-tidal gases with little disturbance of ventilation as indicated by stable arterial blood gas measurements during spectrometer sampling. In addition, there was no dilution of end-tidal gases over the 1-minute sampling period as indicated by a constant quantitative level of end-tidal gases.

Equilibration of anesthetic gases was verified at the conclusion of the 120-minute stabilization period and following each anesthetic change. Equilibrium at each anesthetic level was defined as end-tidal samples of anesthetic gas(es) at 5-minute intervals that differed by less than 5% over a 20-minute period. Each sampling period was 1 minute in duration. MAC was determined utilizing the tail clamp method (11). Briefly described, at the conclusion of each equilibration period, the rat was stimulated near the base of the tail by applying a full length hemostat (20 cm) to the full ratchet position. During a 60-second period of continuous movement of the hemostat, the rat was observed for the presence or absence of purposeful movement. Responses not qualifying as purposeful movements included a twitch, grimace, coughing, swallowing, stiffening, shivering, or a change in the respiratory pattern. The end-tidal enflurane concentration was increased by 10% if purposeful movement (negative drug effect) was elicited and was decreased by 10% in the absence of purposeful movement (positive drug effect). Before additional stimulation, equilibrium at the new enflurane concentration was verified as described before (a minimum of a 20-minute period). In each subsequent stimulation, the enflurane concentration was either increased or decreased by an additional 10% increment until a 10% interval had been bracketed by a positive and a negative response. The midpoint of this last interval was then tested, and by this means the bracketed interval was narrowed to 5% of the original enflurane concentration. An additive MAC was then defined as the end-tidal concentration of enflurane (and N_2O) midway between the highest concentration of enflurane with a positive response and lowest concentration of enflurane with a lack of a positive response. A group MAC for each N_2O concentration was then determined by averaging the individual enflurane

Table 1. Measured Physiological Data (mean ± SD) for Groups I–VI (N = 14)

	Group I	Group II	Group III	Group IV	Group V	Group VI
Age (days)	81.4 ± 7.9	85.2 ± 2.7	85.2 ± 6.5	84.4 ± 6.5	84.7 ± 4.5	81.6 ± 4.6
Weight (g)	237.1 ± 13.2	333.0 ± 10.4	326.3 ± 11.6	330.9 ± 15.7	333.6 ± 14.2	325.4 ± 1.9
pH (U)	7.42 ± 0.04	7.42 ± 0.02	7.43 ± 0.02	7.44 ± 0.05	7.42 ± 0.02	7.43 ± 0.02
PaO_2 (mm Hg)	124.7 ± 16.9	117.8 ± 11.6	130.4 ± 14.4	129.5 ± 17.6	95.4 ± 3.2*	75.3 ± 7.4*
$PaCO_2$ (mm Hg)	40.5 ± 4.4	38.4 ± 2.6	37.9 ± 2.2	38.8 ± 4.1	38.4 ± 2.0	39.0 ± 1.9
End-tidal CO_2 (mm Hg)	38.1 ± 4.2	36.2 ± 2.5	35.9 ± 2.2	36.2 ± 3.8	35.8 ± 2.0	36.8 ± 1.9
Hematocrit (%)	44 ± 3	44 ± 2	43 ± 2	45 ± 2	44 ± 2	44 ± 2
Mean arterial pressure (mm Hg)	87 ± 5†	91 ± 6	96 ± 5†	93 ± 5	94 ± 5†	94 ± 7†
Study time (minutes)	167 ± 13	167 ± 13	167 ± 17	171 ± 20	174 ± 12	175 ± 18

*Statistically significant difference between groups V, VI and other four gorups; and between group V and group VI (P < 0.05); †statistically significant differnece between group I and groups III, V, and VI (P < 0.05).

Table 2. Additive MAC Values (mean ± SD) for Groups I–VI (N = 14)

	Group I	Group II	Group III	Group IV	Group V	Group VI
Enflurane	2.30 ± 0.17	2.19 ± 0.16	1.85 ± 0.10	1.75 ± 0.10	1.56 ± 0.08	1.54 ± 0.12
N_2O	0.00	10.4 ± 0.3	30.7 ± 0.5	61.8 ± 0.8	71.0 ± 0.5	80.3 ± 0.3

contributions to MAC (plus the average N_2O concentration) for each N_2O group.

The physiological data were statistically analyzed using between groups analysis of variance. When significant differences were found, they were further analyzed using a mean t test comparison with a Bonferroni correction factor (12). The potency of N_2O was evaluated in the following manner: For each N_2O group, a dose-response curve was produced by plotting the enflurane concentrations in intervals of 0.1% versus the percentage of rats with a positive drug effect. A positive drug effect was defined as suppression of movement in response to a painful stimulus. The dose-response curves were tested for parallelism and potency differences using analysis of covariance and a Newman-Keuls Multiple Range test (13). Statistical significance was defined as a P value <0.05.

Results

The physiological data are listed in Table 1. Other than small changes in the mean arterial pressure and the PaO_2, no significant differences were observed. The additive MAC values for each of the six different N_2O concentrations are listed in Table 2. A decrease in the enflurane requirement was observed when the N_2O concentration was increased. The dose-response curves for each N_2O concentration are shown in Figure 1 and were found to be parallel. No significant decrease in the enflurane requirement (potency) was produced by increasing the N_2O concentration from

0–10%, from 30–60%, or from 70–80%. Enflurane requirement was, however, decreased by increasing the N_2O concentration from 10–30% and from 60–70%.

Discussion

The present results do not support the hypothesis that multiple combinations of N_2O and enflurane linearly summate to produce 1.0 MAC. As demonstrated in Figure 1, the slopes of the six dose-response curves were not significantly different. In pharmacological terms, this would be consistent with similar mechanisms for N_2O anesthesia at different enflurane concentrations. Separate from the issue of similar slopes is the issue of the right to left shift in the dose-response curves as the N_2O concentration is increased. If N_2O and enflurane combine in a linear fashion, then the quantitative change in enflurane requirement should predictably depend only on the quantitative change in N_2O concentration. The present data, however, are not consistent with this hypothesis of linear additivity. The most dramatic departure from linear additivity was the 30–60% N_2O interval in which a relatively large change in N_2O concentration produced no significant change in the enflurane requirement.

The concept of strict linear additivity of N_2O and enflurane would hypothesize that if a line of additive 1.0 MAC values were to be constructed using two or more N_2O-enflurane combinations, any other N_2O-

DOSE RESPONSE CURVES OF ENFLURANE
WITH DIFFERENT N₂O CONCENTRATIONS
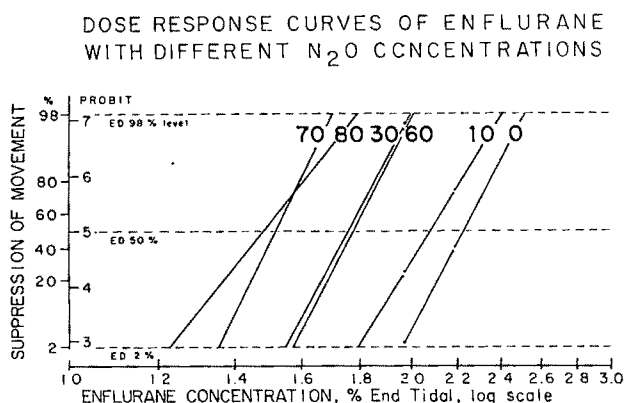
Figure 1. Dose-response curves indicating the percent of rats in which movement was suppressed in the presence of various concentrations of enflurane for 0, 10, 30, 60, 70, and 80% N_2O groups. End-tidal enflurane concentrations are plotted on a logarithmic scale and the distribution of drug response (suppression of movement is displayed with use of probit units [SD]), which are also converted to units of percentage to facilitate interpretation. The enflurane ED50 changed when the N_2O was increased from 10–30% and from 60–70%, but not when increased from 0–10%, from 30–60%, and from 70–80% ($P < 0.05$).
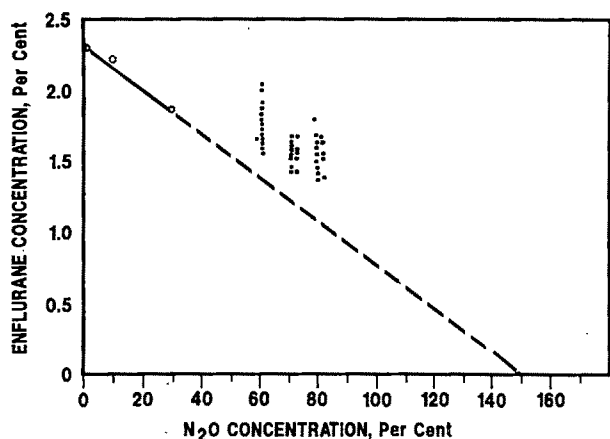
Figure 2. Determinations of enflurane MAC in the presence of various concentrations of N_2O. The solid line and the open dots (O) represent this effect between N_2O concentrations of 0–30%. The dashed line represents an extrapolation of the solid line to a zero enflurane MAC contribution (possible N_2O MAC). Points below this line would correspond to synergism (decreased anesthetic requirement). Points above the line imply antagonism (increased anesthetic requirement). Antagonism was observed in this study for every animal tested with the N_2O concentrations greater than 30% and is represented by the (●) points ($P << 0.001$). See text for further explanation.

enflurane 1.0 MAC combination could be predicted. This concept was tested in Figure 2 by comparing each of the observed enflurane MAC values for the 60, 70, and 80% N_2O group to that predicted by an extrapolated line of N_2O-enflurane additivity using the 0, 10, and 30% N_2O group data points. With use of a least squares estimate (14), a best fit line was drawn through the three lowest N_2O concentrations

evaluated in this study (0, 10, and 30% N_2O) points and extrapolated to its x intercept, which was a predicted N_2O MAC of 150.6%. This predicted N_2O MAC is similar to that predicted by Difazio et al. (8) of 136%. The individual MAC determination for the 60, 70, and 80% N_2O group animals (14 in each group for a total of 42) were compared with the predicted values (of the 0, 10, and 30% N_2O line) with use of a paired t test. The results of the statistical analyses were that the line produced a correlation coefficient of 0.80 ($P < 0.05$), and the three highest N_2O concentrations (60, 70, and 80%) resulted in an enflurane requirement that was significantly higher than that predicted by the extrapolated line ($P << 0.001$). This evidence would tend to contradict the hypothesis of linear additivity, as the best fit line derived from the estimate of enflurane MAC at the three lowest N_2O concentrations (0, 10, and 30%) predicted values significantly lower than those obtained in any of the 42 animals tested for MAC at the 60, 70, and 80% N_2O concentrations. It should be noted that the N_2O MAC extrapolated previously was based on only the 0, 10, and 30% values. If the 60, 70, and 80% N_2O values are incorporated into the extrapolated MAC for N_2O, the 1.0 MAC value for N_2O is 220%.

A possible explanation for the observed results includes a relative antagonism in the anesthetic summation of N_2O and enflurane when N_2O concentrations greater than 30% were utilized. The word relative is a vital concept for if the previously described explanation is correct, N_2O and enflurane may either interact in an antagonist manner when N_2O concentrations greater than 30% were utilized and/or interact in a synergistic manner when N_2O concentrations less than 30% were utilized. It should also be noted that in the present study, this concept would require a nonlinear dose-response curve of these speculative synergistic/antagonistic properties (i.e., if antagonism were present for N_2O concentrations greater than 30%, it would be necessary to invoke an argument that antagonism peaked at a N_2O concentration of 60% where a significant decrease in the enflurane requirement occurred). Although the nonlinear summation in the 0–80% N_2O concentration range is clear, additional studies of N_2O MAC in isolation from other anesthetics must be conducted under hyperbaric conditions to assess whether these results represent an increased enflurane requirement at N_2O concentrations greater than 30% or a decreased requirement at N_2O concentrations less than 30%.

The present observation of nonlinearity may be due to experimental "noise," physiological factors, pharmacokinetic interactions, or multiple drug ef-

fects. In statistical terms, the probability that experimental "noise" (sampling and analysis error, tail trauma, etc.) had an erroneous effect on the observed results is less than 5% ($P < 0.05$). It is also unlikely that a hidden bias resulted in subjective manipulation of the data collection with a consequent perturbation of the enflurane requirement, as the use of a randomized protocol and an all-or-none criterion to define MAC was in effect. Previous determinations of enflurane MAC in the rat have ranged from 2.20–2.50% (15–17). The MAC value of enflurane in the present study (2.30 ± 0.17) was within this range and would tend to validate the methodology of the present study.

One concern when performing MAC studies is the semiquantitative nature of the data. However, MAC determinations are the standard from which anesthetic potencies of volatile agents are measured and provides a reliable and reproducible method of assessing and comparing anesthetic potencies. We attempted to minimize the semiquantitative aspects of the tail clamp method by the following: 1) MAC was defined within a narrow interval (<5% of the volatile anesthetic concentration); 2) Long anesthetic equilibration times (120 minutes initially and 20 minutes for each ensuing enflurane change); 3) Small enflurane changes (<10% of original concentration); 4) Stimulating at the same place on the tail (base). In addition, because of the pilot estimation of MAC, only 3–5 stimulations were required for each rat producing minimal trauma to the tail in the course of the study; and 5) A relatively large number of animals for each group (N = 14).

Several physiological variables are known to influence MAC and could have had a role in producing a nonlinear summation of N_2O and enflurane. These factors include blood oxygen tension, mean arterial pressure, and body temperature (11,18–20). In the present study, multiple physiological indices were monitored and maintained within physiological ranges known not to affect MAC (11,18–20). With few exceptions, no differences were seen between groups. The only observed differences were a reduced oxygen tension and an increased mean arterial pressure for some of the higher nitrous oxide concentrations groups ($P < 0.05$). Decreases in the PaO_2 values are attributed to inspired oxygen concentrations of only 30 and 20% when delivering N_2O concentrations of 70 and 80%, respectively. If this difference had any effect on MAC, the reduced oxygen tension should have decreased the enflurane requirement rather than the observed increase relative to expected linear summation (Fig. 2) (18,19). Mean arterial pressure may have decreased partially as a consequence of dose-related

enflurane hemodynamic effects; however, it is unlikely that the small decrease in mean arterial pressure was a confounding factor, as the observed mean arterial pressure values were within normal clinical limits and did not approach values previously reported to affect MAC (20).

Pharmacokinetic factors may have resulted in decreased central nervous system levels of either N_2O or enflurane, which could explain the observed nonlinearity. However, the attention to equilibration and the careful sampling of end-tidal concentrations of both N_2O and enflurane would suggest that in fact the observed levels of both agents were a reflection of stable brain tissue levels. In addition, our technique for sampling end-tidal gases is supported by a difference of only 2.3 mm Hg between end-tidal and arterial CO_2, suggesting minimal contamination of the end-tidal sampling by ventilatory dead space. Thus, the results reported here are in all likelihood a consequence of the mechanism of anesthetic interaction between enflurane and N_2O.

At least two mechanisms can be postulated to explain the present results. First, because the parameter by which MAC was estimated involved the measurement of an animal's response to noxious stimulation, it is worth noting that both N_2O and enflurane may have analgesic properties independent of their general anesthetic action (21,22). Because there is a possibility of acute tolerance to this dose-related effect (21), it might be considered that tolerance to N_2O may have increased the enflurance requirement. Although this could have been a factor in the nonlinear potency summation of N_2O and enflurane, it must be noted that because anesthetic equilibrium periods were identical in time, it would be necessary to invoke an argument based on preferential development of tolerance at higher N_2O concentrations. This appears to be unlikely (23).

A second possible mechanism by which the present results might be explained is based on observations of excitatory or epileptogenic properties of enflurane. Enflurane has been described to have both cortical-irritant and cortical-depressant properties (24). Although only minimal evidence of epileptiform activity has been reported at levels of 1.0 MAC (approximately 2.5%) enflurane in the rat, higher concentrations produced clear generalized seizure activity (17). Because generalized seizures may have an effect on an animals response to noxious stimulus (either a decrease in response due to post-ictal depression or the possibility of a heightened response due to the stimulating affects of enflurane), the possibility should be considered that enflurane might make contributions to MAC both by a direct anes-

thetic effect and by an excitatory/epileptogenic effect. Epileptogenicity would theoretically be important as an explanation for the present results only if N_2O had the potential to alter this property. In fact, there is evidence in cats that N_2O decreases the epileptogenic effect of enflurane (25). Thus, it may be hypothesized that if enflurane's epileptogenicity and nitrous oxide's anticonvulsant properties are dose-dependent, these factors could combine to produce the observed nonlinear anesthetic summation. However, this explanation is not likely in the present setting. There was no overt seizure activity in any of the rats, and in pilot studies in which the highest enflurane dose used in this study was administered, no seizure activity was observed on electroencephalographic tracings. A more likely explanation is that enflurane can produce both depressant and stimulatory actions in the central nervous system at specific doses. These dose-specific actions of enflurane could interact with similar or opposite dose-specific effects of N_2O in either an inhibitory or excitatory manner to produce the observed nonlinear potency summation. As an example, enflurane has been reported to decrease reticular system firing, whereas activation is observed with N_2O (26,27). Further experiments are needed to test this hypothesis and adequately explain the observed nonlinear summation and determine whether or not this is a unique property of N_2O-enflurane combinations or extends to combinations of other volatile anesthetics and N_2O.

Given the present evidence for nonlinear summation of N_2O and enflurane in the rat, it is important to consider the possibility that similar mechanisms might be in effect during clinical anesthesia. In a human study, Torri et al. (6) compared the effect of two N_2O concentrations on the enflurane requirement to achieve a MAC level of anesthesia. By combining their results with a previously reported enflurane MAC, Torri et al. proposed that N_2O and enflurane are linearly additive. It should be noted that this conclusion was based on the evaluation of two N_2O concentrations and an enflurane MAC value determined elsewhere. Ideally, a definitive statement regarding the summation of these two anesthetics will require testing of multiple combinations in a single clinical study. Comparable studies in animals have provided evidence, in many cases, for nonlinear summation of inhalational anesthetics (8–10), although rigorous statistical analysis was not always performed.

One must be cautious when making clinical assumptions based on animal data. In particular with MAC determinations, it is well known that there are significant interspecies variations (28). In addition,

because of the relative insensitivity of the rat to N_2O (as compared with the human) only the first half of the dose-response curve of N_2O was evaluated (higher concentrations require a hyperbaric chamber). However, when comparing the rat with the human in terms of volatile anesthetic dose requirement, the rat requires a predictable 30% increase in the dose of a volatile anesthetic required to achieve MAC (29). If this correction is applied to the use of N_2O in humans, then these data would predict a nonlinear anesthetic summation of N_2O and enflurane between concentrations of 0–50%, anesthetic levels that are frequently administered. However, until an appropriate clinical study has been completed, this data should only be viewed as a hypothesis.

Nitrous oxide's nonlinear summation raises several salient clinical questions regarding the optimal use of N_2O in regards to such issues as the reciprocal relationship between inspired concentrations of oxygen and N_2O, nitrous oxide's effect on closed air spaces, and N_2O toxicity. If lower concentrations of N_2O produce anesthetic effects commensurate with higher doses, then the use of a lower dose of N_2O would maximize anesthetic effects while minimizing any undesirable side effects.

In conclusion, MAC determinations with six different combinations of N_2O and enflurane demonstrated that the anesthetic combination of N_2O and enflurane did not follow the principle of linear additivity. Although enflurane is not frequently used in contemporary anesthetic practice, this nonlinearity presents an important pharmacologic principle in the use of N_2O in that the anesthetic efficacy of N_2O in combination with a volatile anesthetic may not be as simple as currently taught. Further studies of N_2O with other clinical volatile anesthetics are needed before conclusions addressing the additivity of N_2O in humans can be made.

References

1. Merkel G, Eger EI. A comparative study of halothane and halopropane anesthesia. Anesthesiology 1963;24:346–57.

2. Eger EI, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 1965;26:756–63.

3. Saidman LJ, Eger EI. Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 1964;25:302–6.

4. Munson ES, Saidman LJ, Eger EI. Effect of nitrous oxide and morphine on the minimum anesthetic concentration of Fluroxene. Anesthesiology 1965;26:134–9.

5. Stoelting RK. The effect of nitrous oxide on the minimum alveolar concentration of methoxyflurane needed for anesthesia. Anesthesiology 1971;34:353–5.

6. Torri G, Damia G, Fabiani ML. Effect of nitrous oxide on the anesthetic requirement of enflurane. Br J Anaesth 1974;46:468–72.

7. Stevens WC, Dolan WM, Gibbons RT, et al. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 1975;42:197–200.

8. Difazio CA, Brown RE, Ball CG, Heckel CG, Kennedy SS. Additive effects of anesthetics and theories of anesthesia. Anesthesiology 1972;36:57–63.

9. Eisele PH, Taklen L, Eisele JH jr. Potency of isoflurane and nitrous oxide in conventional swine. Lab Anim Sci 1985;35:76–78.

10. Tranquilli WJ, Thurmon JC, Benson GJ. Anesthetic potency of nitrous oxide in young swine (sus scofa). Am J Vet Res 1985;46:58–60.

11. Quasha AL, Eger EI, Tinker JH. Determination and applications of MAC. Anesthesiology 1980;53:315–34.

12. Program P7D. In: Dixon WJ, ed. BMDP Statistical Software. Los Angeles: University of California Press, 1981.

13. Zar JH, ed. Biostatistical Analysis. 2nd ed. Englewood-Cliffs, NJ: Prentice-Hall, 1984:185–205.

14. Ref. 13, 263–8.

15. Baden JM, Kundomal YR, Luttropp ME jr, Maze M, Kosek JC. Effects of volatile anesthetics or fentanyl on hepatic function in cirrhotic rats. Anesth Analg 1985;64:1183–8.

16. Mazze RI, Rice SA, Baden JM. Halothane, isoflurane, and enflurane MAC in pregnant and nonpregnant female and male mice and rats. Anesthesiology 1985;62:339–41.

17. Myers RR, Shapiro HM. Local cerebral metabolism during enflurane anesthesia: identification of epileptogenic foci. Electroencephogr Clin Neurophysiol 1979;47:153–62.

18. Cullen DJ, Eger EI. The effects of hypoxia and isovolemic anemia on the halothane requirement (MAC) of dogs. I. The effects of hypoxia. Anesthesiology 1970;32:28–34.

19. Cullen DJ, Cotev S, Severinghaus JW, Eger EI. The effects of hypoxia and isovolemic anemia on the halothane requirement (MAC) of dogs. II. The effects of acute hypoxia on halothane requirement and cerebral surface pO_2, pCO_2, pH, HCO_3-. Anesthesiology 1970;32:35–45.

20. Tanifuji Y, Eger EI. The effect of arterial hypotension on anaesthetic requirement in dogs. Br J Anaesth 1976;48:947–52.

21. Berkowitz BA, Finck AD, Ngai SH. Nitrous oxide analgesia: reversal by naloxone and development of tolerance. J Pharm Exp Ther 1977;203:539–47.

22. Finck AD, Ngai SH, Berkowitz BA. Antagonism of general anesthesia by naloxone in the rat. Anesthesiology 1977;46:241–5.

23. Finck D. Nitrous oxide analgesia. In: Eger EI, ed. Nitrous Oxide/N2O. New York: Elsevier Science Publishing, 1985:45–8.

24. Stockard JJ. Cerebral irritant properties of enflurane and isoflurane: modification by carbon dioxide and anesthetic adjuvants (thesis). San Diego: University of California, 1976:56–117.

25. Stevens JE, Oshima E, Mori K. Effects of nitrous oxide on the epileptogenic property of enflurane in cats. Br J Anaesth 1983;55:145–53.

26. Mori K, Winters WD, Spooner CE. Comparison of reticular and cochlear multiple unit activity with auditory responses during various states induced by anesthetic agents. Electroencephogr Clin Neurophysiol 1968;24:242–8.

27. Mori K, Winters WD. Neural Background of Sleep and Anesthesia. Int Anesth Clin 1975;13:67.

28. Steffey EP, Eger EI II. Nitrous oxide in veterinary practice and animal research. In: Eger EI, ed. Nitrous Oxide/N2O. New York: Elsevier Science Publishing, 1985:306–12.

29. Drummond JC. MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: and a test for validity of MAC determinations. Anesthesiology 1985;62:336–8.

The Role of Length of Nerve Exposed to Local Anesthetics in Impulse Blocking Action

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The quantitative relation between the concentration of local anesthetic (LA), the length of nerve exposed, and severity of conduction blockade was studied with use of a chamber where exposure length was varied as the concentration of lidocaine was held constant. Recordings of the compound action potential and of single axons established that small variations in the length of nerve exposed to LA strongly modulate conduction block even at exposure lengths in excess of 2 cm. Therefore, exposure length is a significant factor in determining blocking potency, and only at very high concentrations of LA, where voltage-dependent Na conductance is almost completely blocked, is the critical exposure length less than three nodes of Ranvier. The concentration required for 50% block of impulses in single fibers (that is, where 50% of the impulses would fail to propagate through the exposed region of the nerve) diminished as the exposed length of nerve increased, approximately halving as exposure length was changed from 6 mm to 15–25 mm. Conduction latency increased with the exposure length becoming sharply more variable as the critical exposure length for conduction block was approached. The results are consistent with the hypothesis of decremental conduction, where a partial active response in nodes exposed to marginal blocking concentrations extends the decay of the action potential along the axon, and do not support the interpretation that lengths of several centimeters affect blocking concentration because such distances increase the probability that three nodes will be blocked in succession. This study contradicts the broader common assumption that beyond three nodes, the length of nerve exposed is not a factor in nerve block with local anesthetics.

Key Words: ANESTHETICS, LOCAL: lidocaine, mode of action. NERVE, AXONAL BLOCKADE.

Axonal impulse blockade by local anesthetic (LA) follows from the inhibition of voltage-gated ion channels. Therefore, the impulse blocking potency of LA depends on factors that modulate the inhibition of ionic currents or on other factors, such as the length of axon exposed to the drug, that govern the effects of the weakened currents on impulse propagation.

With high concentrations of LA sufficient to reduce voltage-gated sodium conductance nearly to 0, no more than three nodes of single isolated myelinated fibers (Figure 1) need to be exposed to block propagation of impulses (1).

Passive decay of transmembrane voltages with distance along axons is analogous to the exponential decay that occurs in linear cables and is characterized by the space constant λ, giving the length over which membrane voltage (V_m) decays by a factor of e^{-1} (~37%). Even for large diameter fibers, λ is on the order of 1 mm, which is roughly similar to the distance between nodes (2). Therefore, completely passive spread of V_m during an action potential in a length of nerve sufficient to include two to three inactive nodes would be insufficient to depolarize an adjacent active section of axon to threshold, and the impulse would be blocked.

These facts have greatly influenced the study of LA blocking action, even under conditions in which low concentrations just sufficient for marginal block have been used (3). In particular, it is often assumed that exposure lengths including three nodes suffice for testing anesthetic potency (4,5,6) and that chambers 1 cm long have a comfortable margin in exposure length because internodal distances, even in the largest mammalian nerve fibers, are very rarely as
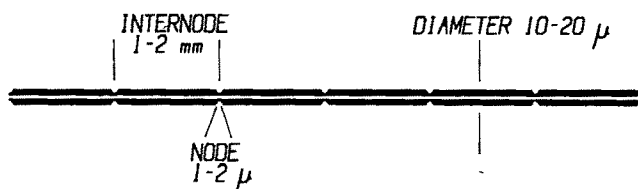
Figure 1. Diagram of a myelinated nerve fiber.

Figure 2. Diagram of the experimental chamber, nerve support system, and data acquisition system. Note the movable baffle with air seal on the left boundary of the exposure well that was used to vary the length of nerve exposed to anesthetics placed only in the exposure well.

great as 2 mm (7). Because space constants for small myelinated and unmyelinated fibers are even less than those for large myelinated axons, exposure length in the range above 6 mm is not usually considered an important determinant of blocking potency across the fiber spectrum.

However, at marginal concentrations of LA, the partial active response of nodes in the exposed region may extend the length of axon over which an action potential decays (8,9), increasing the distance over which exposure length could modulate conduction (10,11). Recently, Fink and Cairns (12) have argued that lengths of "several cm" may influence block under "unfavorable" clinical conditions, even though concentrations of lidocaine injected in nerve blocks (for example, 1% $\approx$ 40 mM) exceed marginal blocking concentrations by a factor on the order of 100. This argument was based on an alternative idea to decremental conduction (4), that the probability of three successive nodes each being exposed to its minimal blocking concentration was contingent on local variations in pharmacokinetics and anatomy, thereby requiring exposure of many nodes to ensure that three successive ones be blocked.

We sought to study these issues by quantitating the relations among degree of block, the concentration of anesthetic, and the length of nerve exposed to LA.

Methods

Frog sciatic nerves were extracted from pithed 3–5 in. Rana pipiens or 4–7 in. Rana catesbeiana (snout to vent) and bathed in a Boyle-Conway saline-glucose solution bubbled with 5% CO_2 in air, containing in mM: NaCl 80.5, KCl 2.1, $CaCl_2$ 1.8, $MgSO_4$ 1.2, Na_2SO_4 0.66, $NaHCO_3$ 25.0, Na_2HPO_4 2.6, KH_2PO_4 0.5, glucose 3.3. Three wells in the plexiglass nerve chamber (Figure 2) were circulated separately. One wall of the exposure chamber was tapped for a fine-pitch lead screw and could be moved. Vaseline seals prevented fluid exchange between the stimulation well and the central exposure well. At the other end of the exposure well, a 4-mm gas bearing seal inflated with a threaded piston prevented lidocaine
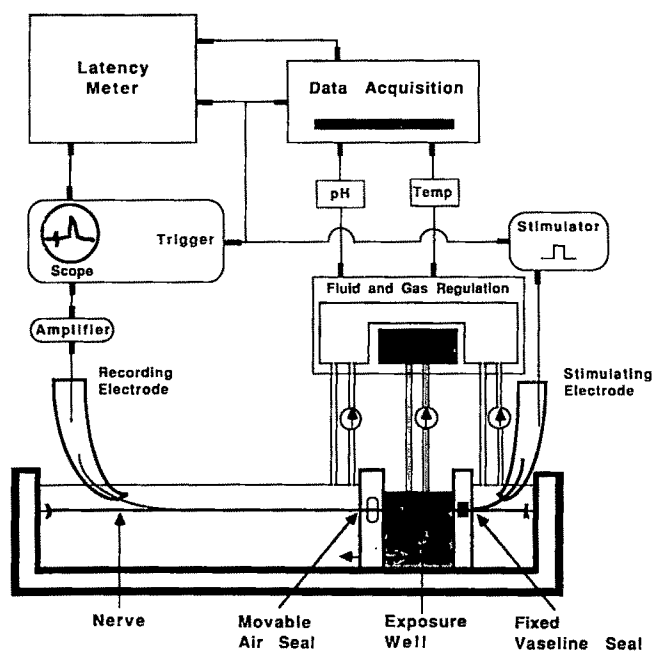
from escaping into the recording chamber. The sciatic nerve trunk, sheath intact, under slight tension just sufficient to prevent sagging, passed through the center of the seal and was thus surrounded by the gas mixture (5% CO_2 in air). When the wall was moved, the seal moved with the wall and the nerve itself was not perturbed.

No anesthetic was administered to solutions circulating in the recording or stimulating wells. Recording of small filaments containing 1, 2, or 3 active single fibers or of large branches of the nerve allowed us to compare results from compound action potentials (CAP) with impulses in single axons. Stimuli were delivered at the central end of the nerve trunk through a closely fitting suction electrode. For CAP, the stimulus intensity was held at 1.5 times the supramaximal level. For single units, stimuli were 5 times threshold intensity for the fiber.

CAP. The CAP was recorded by plastic suction electrodes placed so that even at the longest exposure distances, at least 1 cm of the nerve branch in the recording well was exposed to the lidocaine-free saline solution. This procedure ensured that any decrease in CAP amplitude was due either to blockade of axons (impulse extinction) in the exposure well or to temporal dispersion among the unit potentials constituting the CAP. Exposure to LA of the recorded region would have reduced the amplitude of the

active currents (13) and would thus suppress the CAP directly, even in the absence of block or dispersion. Lidocaine was added to the supply vessel for fluid circulating through the exposure well (total volume 77 ml), and a fixed concentration was maintained throughout the experiment. CAP waveforms were monitored in response to stimuli given every 2 sec and to short trains 2 sec long given alternately every 30 sec at 5 and 50 Hz. The heights of the CAP were visually measured on a Tektronix storage oscilloscope and noted every 1 min as the exposure distance was extended and shortened.

Single axons. Fibers or small fascicles were teased from the distal end of the nerve and recorded with flexible suction electrodes drawn to 20–40 μ tips. Blocking concentrations (concentrations sufficient to prevent conduction in response to 50% of the stimuli given at 2-sec intervals) were measured in two ways: by adjusting exposure length at fixed (LA) or by adjusting (LA) at a fixed length. Single unit potentials were windowed to an analog latency meter that measured the delay from the beginning of the shock artifact to the transition of a Schmitt trigger set to trigger during the fastest rising segment of the unit potential in the window. Lidocaine (courtesy of Astra Pharmaceutical Corporation) was freshly dissolved for each experiment into 2 ml (38 mg/ml = 141 mM) distilled water and diluted into the saline solution as required. In 14 fibers, a form of lidocaine (LX) with 4–5 times the effective potency of lidocaine HCl was used, and the results of 29 critical length determinations were quite similar to those obtained in 22 fibers with 42 critical length determinations with use of lidocaine HCl. Except for the example of a critical length determination in Figure 3, however, we have included here only data obtained with lidocaine HCl.

Latencies were recorded at 5-μsec resolution and were also monitored digitally at 0.1 μsec resolution. Latencies and occasional single unit potentials were stored to disk on a Computer Automation (Richardson, TX) Scout minicomputer and were plotted with use of a Watanabe (Western Graphtec, Newport, CA) x-y digital plotter. The temperature was held at 16.5 ± 0.5°C by a Peltier thermal controller (Cambion, Solana, CA). The pH was maintained at 7.3 ± 0.2 by controlling the proportion of CO_2 in the gas mixture.

In initial experiments, the quality of the air bearing seal was monitored by tracking the electrical resistance between exposure and recording pools; later, occasional visual inspection of the bubble was found to suffice. In three experiments, the presence of lidocaine in the recording pool was checked hourly
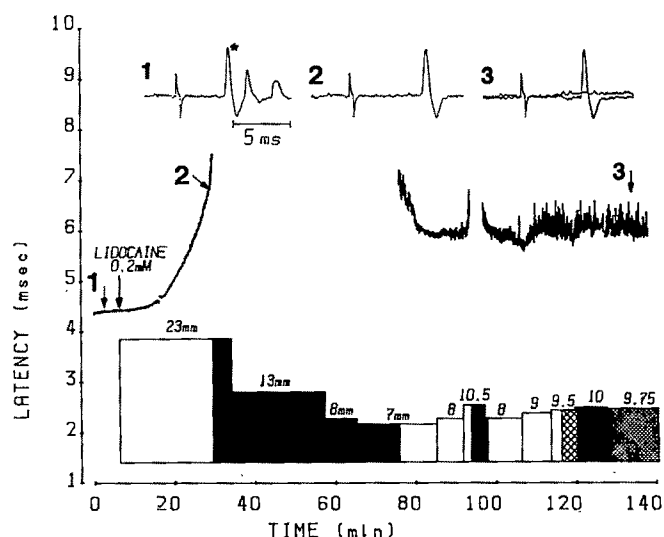
Figure 3. Determination of a critical length. The top of the figure shows the unit action potentials. The middle section shows the latency of each successfully conducted impulse (as measured for the fast conducting potential marked by a star in the first trace) throughout the determination (140 min) vs. time. The numbers on the curve indicate when samples of the unit potentials displayed above were taken. At the bottom there is an index showing the exposure length. The density of hatching reflects the probability of conduction: 100% = white; 0% (that is, complete block) = black; 50% = gray. Degrees of gray indicate more or less than 50%. Lidocaine (ASTRA LX, ~4 times potency of Lidocaine HCl) was added at 22-mm exposure length leading to slowing and block. Reducing the exposure length (same concentration of LA) restores 100% conduction. Fifty percent conduction was approached by adjusting the length progressively more finely over the next hour resulting in the determination of critical length at 9.75 mm. Small (± 100μ) changes from this length strongly shifted the probability of conduction. Note the nine-fold increase in the range of fluctuations in latency at critical length vs. unexposed control conditions. (Fiber conduction velocity 12.4 m/sec)

with use of gas chromatography. The concentration was less than 1% of the lidocaine level in the exposure well even after as long as 8 hours.

Results

Compound Action Potentials

Large myelinated axons contribute to the first elevation of the CAP. Recorded with suction electrodes, this elevation was a predominantly monophasic positive deflection ranging between 5 and 20 mV in amplitude. The amplitude depended on the precision of fit of the electrode to the nerve branch sucked into it and on the mechanical stability of the nerve within the electrode, rising or declining if the nerve were sucked further into the electrode or fell out of it. In 27 experiments with nerves from Rana pipiens (N = 22) and Rana catesbeiana (N = 5), we achieved sufficient stability that the CAP height remained within ±3% of

control values for several hours. Lidocaine was applied to segments of the nerve ranging from 5–50 mm in length.

At a fixed concentration of lidocaine, the tonic CAP (sampled every 2 sec) decreased in amplitude as the exposure distance was increased. The exposure length was changed in a stepwise manner with each step taking about a minute to complete. The tonic CAP then continued to change for 10–15 minutes afterward as the lidocaine equilibrated with the freshly exposed segment of nerve (if exposure length had been increased) or diffused away from a previously exposed segment (if exposure length had been decreased). Without lidocaine, moving the air bearing had negligible effect on CAP height. A further attenuation of the CAP occurred with repetitive stimulation with short trains of stimuli (40–100 pulses) at 5 and 50 Hz, both during the onset transients and at steady-state. This "phasic" drop in CAP height and the tonic drop were both reversed when the exposure length was shortened (Figure 4). Without exception, such shortening tended to restore the CAP amplitude.

The CAP was reduced significantly by increases in exposure length even above 20 mm (Figure 5). The CAP amplitude could be set between 80 and 20% of control levels simply by adjusting exposure length without altering concentration of local anesthetic or the overall conduction distance.

However, some flattening of the CAP could be due to differential slowing among the several hundred fibers whose individual action potentials add to form the CAP (12,14) and may not, therefore, reflect actual conduction failure. Because the recording was made from a segment of the nerve that was *not* exposed to local anesthetic, no diminution of CAP due to direct effects on the unit action potentials at the electrode can account for the drop of CAP.

Single Fibers

To investigate differential slowing of impulses in different axons and to confirm that the impulse *conduction failure* implied by the drop in CAP actually occurred, we recorded from single fibers in nerves exposed to local anesthetic. Such fibers show block as an absence, not an amplitude reduction, of an action potential. We defined the critical exposure length for conduction failure in any particular fiber as the length where only 50% of the stimulated impulses (at 0.5 Hz) were detected on the other side of the exposure well. This "critical length" was a strong function of local anesthetic concentration.
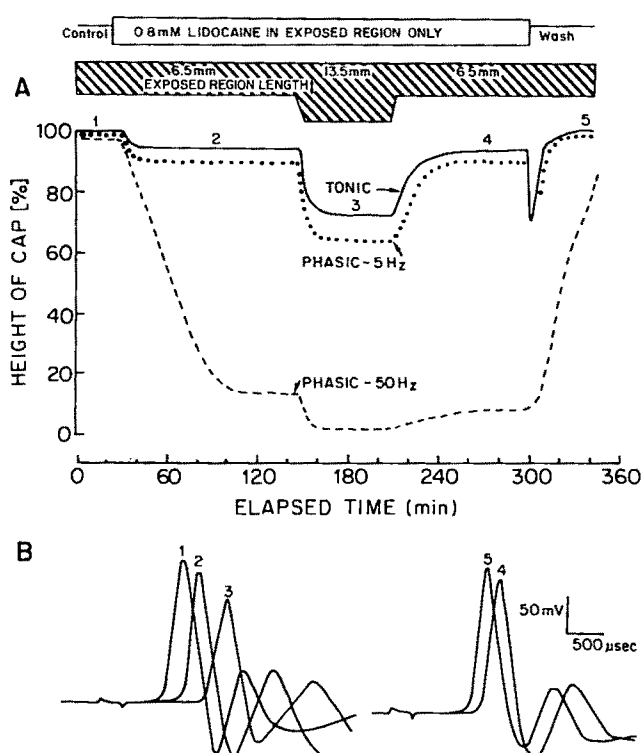
Figure 4. Changes in CAP amplitude during exposure to 0.8 mM lidocaine in one experiment. A, The top legends show the time of application of lidocaine and the extension and shortening of the exposure well (hatched region). Note the rapid development and relatively later recovery of phasic block. The transient drop in CAP amplitude with washing on the far right reflects the high initial PCO_2 (30%) in the wash solution before it equilibrates with the gas supply (5% CO_2 in air). The numbers above the CAP amplitude denote timing of the photographs of the tonic CAP traced in B. The CAP during exposure and increased exposure length (left) is similar to the CAP during shortening and wash (right).

Critical lengths were measured by stepping the concentration of LA in the exposure pool to a new level and adjusting the exposure length until 50% of the impulses failed to propagate through the exposure pool. This was a surprisingly precise measurement (Figure 3), resolved to fractions of a millimeter (0.25–0.5). Even at the lower range of concentrations, where critical lengths were more than 20 mm, 1-mm changes in exposure length strongly influenced the probability of conduction through the exposed regions of axon. In four experiments, a critical length measured early at one concentration was measured again several hours later after re-equilibration with the initial concentration of LA. Repeatability of the critical length was within ±15% and averaged +12% (+0.9 mm).

During the successive approximations of exposure length to critical length, the latency in impulse conduction becomes quite variable as the critical length is approached. The range of latency fluctuations around the average latency at 5 times threshold stimulus

Figure 5. CAP amplitude declines with length of nerve exposed to lidocaine (0.8 mM). The data are from one experiment with a nerve from a large bullfrog that was long enough to test for continued decline of the CAP for exposure lengths beyond 35 mm. Amplitude expressed in percent of the unexposed control amplitude.
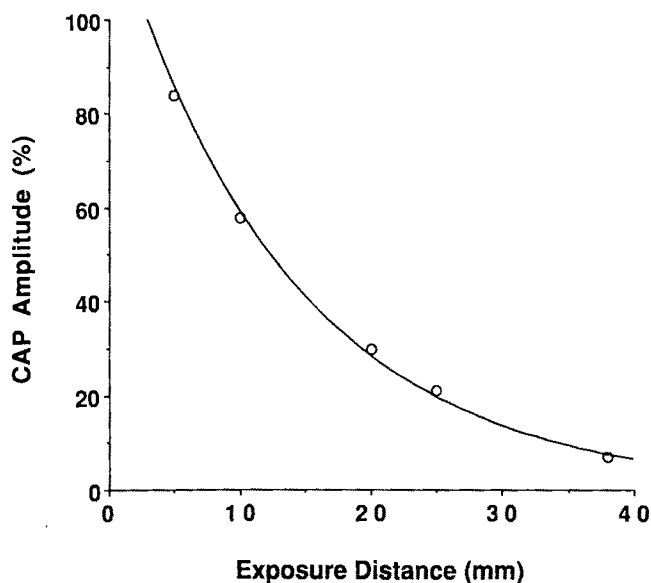

Figure 6. Serial measurements of critical length at several concentrations of lidocaine HCl. The separation of the curves reflects differential tonic (sampled at 0.5 Hz) susceptibility to lidocaine. The range of each curve shows that variations of exposure length counts for a factor of 1.5–2 in concentration with as much as 50% of the effect deriving from changes in length in the domain above the commonly used 1-cm exposure distance.

intensity was slight ($< \pm 250$ μsec) under control conditions and grew by as much as twelvefold ($+1500$ and -300 μsecond) at critical length (for example, in Figure 3). Similar latency "noise" with a distribution skewed strongly toward increased delay occurs during electrical stimulation at threshold level (15) and was interpreted here as a sign of approach to critical length.

The process of determining a critical length, which required 2 or more hours for equilibration, was repeated for a given fiber at several concentrations of lidocaine. This process was successfully achieved for three or more critical length determinations in each of six fibers with lidocaine HCl and in three fibers with the higher potency lidocaine. This evidence, graphed for lidocaine HCl in Figure 6, shows that at short exposure lengths, more than twice as much anesthetic was required than that at the longest exposure lengths (25–35 mm); that each fiber has a monotonic relation between exposure length and blocking concentration of lidocaine; and that the curves differed, revealing the intrinsic differential susceptibility of the individual fibers to LA.

Fiber Differences

It is clear in Figure 6 that over the range of exposure lengths explored (5–30 mm), the rank order of susceptibility to lidocaine among the six fibers did not differ. However, the slopes of the curves did differ,

indicative of differences in sensitivity to LAs, and the possibility remains that had more fibers been investigated the curves with shallow slopes would have crossed curves with steeper slopes, making the rank order of susceptibility contingent on the exposure length. For the 22 fibers ranging in conduction velocity from 5–24 m/sec, in which 42 critical lengths were measured with lidocaine HCl, there was no significant relation between rest conduction velocity (axon diameter) and susceptibility to LA (Figure 7), even at short exposure lengths. As might be expected from the findings from the CAP, there was a trend in the lumped data from faster fibers toward lower blocking concentrations at longer exposure lengths (Figure 8A). Drawing lines connecting the successive measures in single fibers (Figure 8B) emphasizes the trend.

Discussion

Exposure Length Affects Blocking Dose Beyond Three Nodes

The length of nerve exposed to LA affected the amplitude of CAP and the blocking concentration for single axons over a range extending from 6 to beyond 30 mm. Because the internodal distances in amphibian (and mammalian) myelinated fibers are on the order of 1 mm, this finding implies that the blocking concentration will depend on exposure length over a range in excess of 20 nodes. Moreover, when the

Conduction Velocity (m/sec)
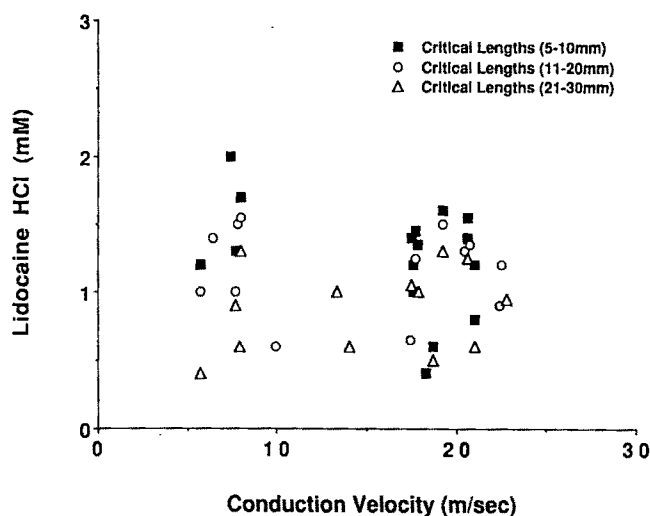
Figure 7. Blocking concentration of lidocaine HCl vs. rest conduction velocity over the range of exposure length. Forty-two blocking concentrations were determined for 28 fibers. The highest concentrations required were to block two fibers conducting under 10 m/sec through short (<10 mm) exposure length. No relation was found between susceptibility to block by lidocaine and resting conduction velocity (proportional to axon diameter).

concentration of anesthetic was just below the critical blocking level, the incremental effect of adding 1 mm to a 25-mm exposure length was sufficient to block fibers conducting with 100% success before the extension. Such observations imply either that impulses decrement progressively during conduction through a region of axon exposed to LA or that there are particular sites along an axon that are relatively more prone to LA block, which are always encountered when the exposure length is incrementally increased.

These results show that at any given concentration of lidocaine there is a *direct* relation between the incidence of block in a fiber population and the length of nerve exposed to LA. Therefore, our results are in contradiction with the claim of Fink and Cairns (12) that "incidence of block was an inverse function of length of nerve in contact with the drug." However, the relevant data in their study (their Table 1) show a greater number of single units blocked by 0.6 mM lidocaine at longer exposure lengths (39% blocked at 5 mm and 75–96% blocked at exposure lengths above 23 mm). Furthermore, in their discussion, they offer an explanation for a *direct* relation between exposure length and incidence of block, which makes us believe that our direct measurements of critical length in frog sciatic fibers are, in fact, consistent with their survey of blocking incidence at 0.6 mM lidocaine in rabbit vagal and recurrent laryngeal nerve fibers.

At long exposure lengths, the slope of the relation between exposure length and blocking concentration for each fiber appears to approach a vertical asymptote (a minimal blocking concentration) that is well

above zero concentration (Figure 6). This minimal blocking concentration reflects the intrinsic conduction safety of each fiber and is an appropriate index of relative susceptibility to LA at steady state among fibers. It avoids the complication of the dependence of blocking potency on exposure length because further increases in exposure length negligibly affect the blocking concentration. The notion that fibers differ intrinsically in conduction safety (5,16) rather than in probability that 3 adjacent nodes will be blocked (4) is the likely basis of differential block (3).

At the opposite extreme, short exposure lengths dramatically increase the dose of anesthetic required to block fiber conduction. At exposure lengths of 2–3 mm, the dose should rise without limit, expressing the capability of the impulse to conduct through one or two, but not three, completely unresponsive nodes (1). In our experiments, 5-mm exposure lengths were the minimum we could achieve, and near such short lengths (5–7 mm) a blocking dose could be found, although at 1–2 mM these doses were as much as 5 times greater than the least dose required to block the most susceptible fibers at longer exposure lengths.

Impulse Conduction in the Exposed Region

An important distinction between two images of saltatory conduction failure with local anesthetics can be made on the basis of these results. In one image, a blocked node is considered to have no active regenerative currents, and conduction fails whenever circumstances (physical barriers, concentration gradients, sufficient time from injection, and so forth) permit three successive nodes to be blocked (4,6,12). In the other image, all nodes exposed to marginal blocking concentrations of LA are capable of an attenuated active response. A series of identical nodes exposed to the same concentration of LA results in a progressive decrement in the action potential because each successive node is driven by a weaker action potential and generates an incrementally weaker response to drive the next node (9). In this view, conduction fails when the attenuated response is too weak to depolarize the next node, and the local response then falls nearly to 0 over the next three to five internodal lengths.

The results summarized in Figure 6 do not show a discontinuous or sudden relation between exposure length and blocking concentration, and at each critical length, small changes in exposure length shifted the probability of conduction quite steeply. This occurrence supports the model of decremental conduction (8) throughout the exposed region. The alter-

Figure 8. Blocking concentration of li-
docaine HCl vs. exposure length. **A**,
The blocking concentrations for fibers
that would contribute to the first eleva-
tion of the CAP (Conduction velocities
>17 m/sec) are plotted vs. the exposure
lengths at which the blocking concen-
trations were determined (critical
lengths). **B**, Successive measures from
the same fiber are connected. Extrapo-
lation of the curves for two measure-
ments/fiber was done on the basis of the
similarity of curves in Figure 6 to esti-
mate the cumulative failure of fast units
with exposure length at 0.8 mM lido-
caine HCl (see text).
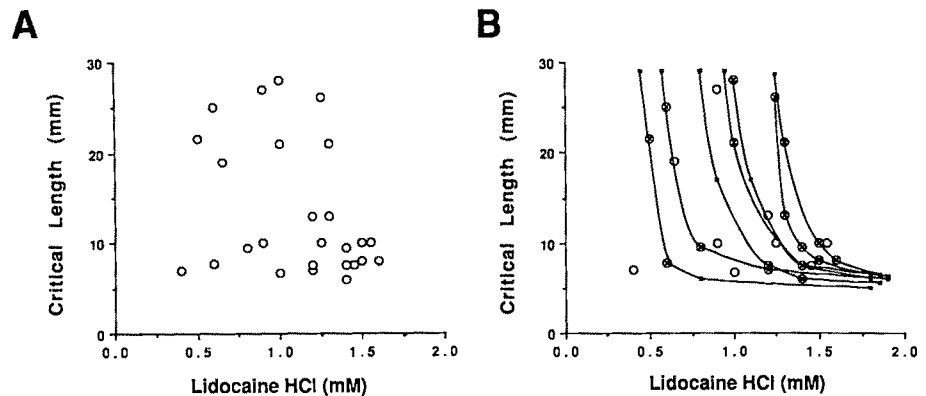
native hypothesis of randomly distributed sites of
varying degrees of low conduction safety implies that
sometimes a site of quite low conduction safety
would have been located within the initial 6–8 mm of
exposure. Lowering the anesthetic concentration
would then have had no effect on subsequent mea-
sures of critical length until the concentration
dropped below the minimal blocking concentration
for the site. A slight further reduction of local anes-
thetic might then have dramatically increased the
measured critical length. However, we always ob-
served slight increases in critical length with slight
decreases in lidocaine concentration and larger in-
creases in critical length with larger decreases in
concentration, supporting homogeneity along the
axon of both conduction safety and susceptibility to
anesthetic. Tracking excitability of successive nodes
along a fiber is known to show no discontinuities in
firing threshold, and any one fiber's nodes are also
quite similar to each other in the degree of change in
electrical excitability with repetitive discharge (2). We
also know from many investigations that ion chan-
nels in nerve membrane are progressively inhibited
by increasing doses of local anesthetic (13,17,18) and
that axonal action potentials are also decreased in a
parallel, progressive manner (19). If all the nodes of a
given fiber are nearly equivalently affected by expo-
sure to lidocaine, as such evidence suggests, then we
must look for a progressive diminution of the driving
current as the action potential propagates through
the exposed region to explain the increase in block
resulting from extending the exposure length.

Models of impulse conduction based on the pre-
sumption that nodes have identical properties show
that the driving currents from impulses in nodes at
the beginning of the exposed region decline progres-
sively until they are just barely unable to sustain
propagation of the impulse (9). Our experimental
evidence suggests that this region of decrement can
extend beyond 20 successive internodes, which ex-
ceeds the range of 10 nodes explored by Condouris et

al. (9) in mathematical models of myelinated fibers
where exposure to lidocaine or tetrodotoxin was
simulated.

The increased variance in latency that occurs when
exposure length is near the critical value for blocking
conduction, which also occurs in mammalian fibers
(4), resembles in range and distribution the increased
variance in latency seen during electrical stimulation
of axons at threshold level (15). It can be attributed to
fluctuations in the firing time of the first unexposed
node after the exposure pool. It is consistent with the
model of decremental conduction that this node
would be driven just barely to threshold by the action
currents of the diminished spike at critical length.

Fiber Differences

Differential block as a function of diameter has mainly
been observed under conditions where the exposure
length is 10 mm or less (5,4,review 3). Studies on
single fibers using exposure distances up to 60 mm
have found little relation between size (inferred from
conduction velocity) and susceptibility to anesthetic
(3,4,12). In the present study, slower conducting
myelinated fibers were not more susceptible to lido-
caine block over the range of exposure lengths used
(Figure 7), which does not support the prediction of
Raymond and Gissen (3) that slow fibers would be
more susceptible than large, fast-conducting fibers at
shorter exposure distances. However, although inter-
nodal distances are broadly correlated with diameter
over a range of 2–18 μ (20), variation in internodal
length is great among mammalian fibers (7). And
between 11 and 20 m/sec no correlation was found in
frog fibers between internodal length and conduction
velocity (2). In the face of the large interfiber varia-
tions, our present sample size of serially tested single
fibers is not sufficient to disprove the hypothesis (3,4)
that size related differential susceptibility of slow
fibers to block emerges only at short exposure

lengths. Because nociceptors are coupled to smaller axons than those studied here, these results thus do not rule out the possibility of producing strongly differential local anesthetic block for pain by restricting the exposure length.

Interfiber variation makes serial measures in single fibers more discriminating for pharmacological effects than population studies across fibers. This point is emphasized in this study by the broad scatter of the lumped population data in Figure 8A, where variations in tonic susceptibility among fibers obscures the trend of increased lidocaine required for block at short exposure length. However, the dependence of blocking concentration on exposure length emerges clearly (Figures 6, 8B) when serial measures in individual fibers are linked.

The single fiber data can also be used to analyze the drop in CAP with exposure length. By assuming that an approximate twofold range in blocking concentration results when exposure length is varied between 6 and 20 mm and that the curves expressing the dependence in fast (>17 m/sec) A-fibers are similar to those in Figure 6, we can project the length expected for conduction to fail for each of the fibers in Figure 8B. The cumulative impulse extinction in fast-conducting units is 16, 34, and 44% at 10, 20, and 30 mm exposure distances, whereas the relative reduction of the CAP at these lengths averaged (N = 21) 24, 40, and 49%, suggesting that about 80% of the loss in CAP amplitude is due to block and about 20% to temporal dispersion. Fink and Cairns (12) credit an inappropriately high proportion of the drop in CAP to dispersion because they exposed the nerve at the recording site, which would lower the amplitude directly by reducing the action currents.

References

1. Tasaki I. Nervous Transmission. Springfield, MA: CC Thomas, 1953.

2. Carley LR, Raymond SA. Comparison of the after-effects of impulse conduction on threshold at nodes of Ranvier along single frog sciatic axons. J Physiol (Lond) 1987;386:503-27.

3. Raymond SA, Gissen AJ. Mechanisms of differential block. In: Strichartz GR, ed. Handbook of Experimental Pharmacology Vol. 81: Local Anesthetics. Berlin: Springer-Verlag, 1987;95-164.

4. Franz DN, Perry RS. Mechanisms for differential block among single myelinated and nonmyelinated axons by procaine. J Physiol (Lond) 1974;236:193-210.

5. Nathan PW, Sears TA. Some factors concerned in differential nerve block by local anaesthetics. J Physiol (Lond) 1961;157:565-80.

6. Ford DJ, Raj PP, Pritam S, Regan KR, Ohlweiler D. Differential peripheral nerve block by local anesthetics in the cat. Anesthesiology 1984;60:28-33.

7. Arbuthnott R, Boyd IA, Kalu K. Ultrastructural dimensions of myelinated peripheral nerve fibres in cat and their relation to conduction velocity. J Physiol (Lond) 1980;308:128-57.

8. Lorente de Nó R, Condouris GA. Decremental conduction in peripheral nerve. Integration of stimuli in the neuron. Proc Natl Acad Sci USA 1959;45:592-617.

9. Condouris GA, Goebel RH, Brady T. Computer simulation of local anesthetic effects using a mathematical model of myelinated nerve. J Pharmacol Exp Ther 1976;196:737-45.

10. Raymond SA, Gugino LD, Steffensen SC, Thalhammer JG, Strichartz GR. Critical length: partial impulse block increases with length of nerve exposed to lidocaine. Pain 1987;4(suppl): S384.

11. Raymond SA, Steffensen SC, Gugino LD, Strichartz GR. Critical exposure length for nerve block of myelinated fibers with lidocaine exceeds 3 nodes. Reg Anaesth 1988;13:46.

12. Fink BR, Cairns AM. Lack of size-related differential sensitivity to equilibrium conduction block among mammalian myelinated axons exposed to lidocaine. Anesth Analg 1987;66:948-53.

13. Hille B. Common mode of action of three agents that decrease the transient change in sodium permeability in nerves. Nature 1966;210:1220-2.

14. Dorfman LJ, Cummins KL, Leifer LF, eds. Conduction Velocity Distribution: A Population Approach to the Electrophysiology of Nerve. New York: Alan R. Liss, 1981.

15. Raymond SA. Effects of nerve impulses on threshold of frog sciatic nerve fibres. J Physiol (Lond) 1979;290:273-303.

16. Gissen AJ, Covino BG, Gregus J. Differential sensitivity of fast & slow fibers in mammalian nerve. II. Margin of safety for nerve transmission. Anesth Analg 1982;61:561-9.

17. Narahashi T, Frazier D, Yamada M. The site and active form of local anesthetics. I. Theory and pH experiments with tertiary compounds. J Pharmacol Exp Ther 1970;171:32-44.

18. Ärhem P, Frankenhaeuser B. Local anesthetics: effects on permeability properties of nodal membrane in myelinated nerve fibres from Xenopus. Potential clamp experiments. Acta Physiol Scand 1974;91:11-21.

19. Shanes AM. Electrochemical aspects of physiological and pharmacological action in excitable cells. Pharmacol Rev 1958;10:59-274.

20. Ritchie JM. On the relation between fibre diameter and conduction velocity in myelinated nerve fibres. Proc R Soc Lond 1982;B217:29-35.

Time Course and Hemodynamic Effects of Alpha-1-Adrenergic Bolus Administration in Anesthetized Patients with Myocardial Disease

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SCHWINN DA, REVES JG. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg 1989;68:571–8.

Phenylephrine (Phe) is frequently administered as an intravenous (IV) bolus to increase blood pressure, yet the acute time course and hemodynamic effects of bolus Phe in patients with myocardial disease have not been reported. Therefore 50 randomized IV bolus doses of Phe (50, 100, 150, or 200 µg) were given to 18 patients during anesthesia for elective coronary artery surgery. Esophageal Doppler techniques were used to continuously monitor cardiac output (CO); mean arterial pressure (MAP), CO, and calculated systemic vascular resistance (SVR) were recorded every 5 seconds for a total of 2 minutes. The hemodynamic changes (mean ± SEM) for each of the four doses of Phe (50, 100, 150, 200 µg) were maximal at about 42 seconds after the drug was given. They consisted of an increase in MAP (11.6 ± 2.1, 15.6 ± 2.4, 14.7 ± 2.4, 18.0 ± 1.5 mm Hg); increase in SVR (766 ± 190, 930 ± 310, 950 ± 344, 1732 ± 824 dynes·sec·cm^{-5}); and a decrease in CO (−.58 ± .11, −.68 ± .13, −.73 ± .20, −.77 ± .18 L·min^{-1}). Hypertension, increased age, low preoperative ejection fraction, high baseline CO, and low baseline SVR significantly (P < 0.05) decreased hemodynamic responses to Phe (see text). In conclusion, bolus IV Phe in patients with myocardial disease increases MAP and SVR and simultaneously decreases CO; these peak hemodynamic events occur approximately 42 seconds after Phe administration.

Key Words ANESTHESIA—cardiovascular. RECEPTORS—alpha-1 adrenergic. HEART—coronary artery disease. SYMPATHETIC NERVOUS SYSTEM—pharmacology, phenylephrine.

Phenylephrine, an alpha-1-adrenergic agonist (1,2), is frequently administered as a bolus intravenous injection to increase blood pressure during anesthesia and surgery. While the hemodynamic effects of continuous phenylephrine infusion have been well documented in animals and humans (3–5), the beat-to-beat hemodynamic effects of a bolus dose of phenylephrine have not been reported. On the basis of infusion studies, the mechanism of blood pressure elevation by phenylephrine is increased systemic vascular resistance (SVR) (6). Increases in SVR produced by phenylephrine are particularly important in patients with myocardial disease. In these patients it can be hypothesized that increased afterload resulting from increased SVR may decrease cardiac output, potentially resulting in minimal net blood pressure change. Evaluation of this hypothesis has only recently become possible with advances in esophageal Doppler techniques which permit near continuous monitoring of cardiac output. Therefore we assessed the time course and hemodynamic effects of alpha-1-adrenergic stimulation with bolus intravenous injection of phenylephrine in patients with myocardial disease during coronary artery bypass graft surgery.

Methods

After institutional approval and informed patient consent, 50 bolus doses of (−) phenylephrine HCl (Winthrop Laboratories, New York, NY 10016) were given to 18 patients undergoing elective coronary artery bypass graft surgery. All patients were premedicated within two hours of surgery with intra-

muscular morphine 0.1 mg·kg^{-1}, intramuscular scopolamine 0.2–0.4 mg, and oral diazepam 0.015 mg·kg^{-1}. Oxygen at 2 liters/min was begun at the time of premedication and continued until induction of anesthesia. Patients were anesthetized with various anesthetics including fentanyl, sufentanil, enflurane, and isoflurane; muscle relaxation prior to intubation was accomplished with vecuronium 0.1 mg·kg^{-1} in all patients.

Following intubation of the patient's trachea, a Lawrence L3000 Cardiac Output Monitor® (Lawrence Medical Systems, 1100 Avenida Acaso, Camarillo, CA 93010) probe was placed in the esophagus and positioned until maximal signal level was elicited from blood flow in the descending aorta. Blood velocity in the descending aorta was determined utilizing the Doppler shift of transmitted sound (7,8). In brief, the Doppler principle states that ultrasonic waves transmitted from a probe through the blood stream are reflected with a frequency shift due to moving erythrocytes. In general, reflected frequencies from blood moving toward a stationary probe appear higher, and reflected frequencies from blood moving away from a stationary probe appear lower than if neither object was moving. This change in frequency is called the Doppler shift. Velocity (V) of blood flow in the descending aorta can be determined by the Doppler velocity equation: $V = (c/ 2f_o \cos\theta)(F_d)$ where c = velocity of sound in blood (a constant), f_o = the known frequency of the transmitted ultrasound signal, F_d = Doppler frequency shift, θ = angle of the probe to the blood vessel. In practice, making the probe as parallel to the vessel as possible by making the Doppler signal level as loud as possible, nearly eliminates the unknown θ (if the angle is <20°, cos θ is approximately 1). The equation therefore reduces to the velocity of blood flow in the descending aorta being directly proportional to a constant multiplied by the Doppler frequency shift. In clinical terms, the faster aortic blood moves past an esophageal Doppler probe, the greater the Doppler shift and the higher the recorded cardiac output.

Prior to anesthetic induction, catheters were placed in a radial artery (20 gauge) and in the pulmonary artery (Edwards Swan-Ganz) with a central venous pressure (CVP) port in the mid-right atrium. Mean arterial pressure (MAP) and CVP were monitored using a Marquette Monitor® (Marquette Electronics Inc.). The display of the Marquette Monitor® reflecting mean arterial pressure was updated every two seconds. Cardiac output (CO) was calculated using the equation: Cardiac Output = (Heart Rate)·(Doppler Signal Level)·(Constant). Using research software (version 2.4) supplied by Lawrence

Medical Systems, heart rate (HR) and Doppler signal level were recorded every six heart beats. During calibration, initial cardiac output was measured using the mean of three consecutive thermodilution cardiac output measurements; the constant for each trial was then calculated. SVR is related to MAP, right atrial pressure (RAP), and CO by the equation: SVR = (MAP–RAP)/CO. This product was multiplied by 80 to convert from Woods units to dynes·sec·cm^{-5}.

In each trial, patients were randomized to receive 50, 100, 150, or 200 μg intravenous phenylephrine. Of note, patients were initially randomized to receive only 50 or 100 μg phenylephrine but mid-way through the study when it became apparent that individual bolus doses of 150 or 200 μg phenylephrine could be given safely, these doses were added. Resulting group sizes were as follows: 50 μg Phe, n = 24; 100 μg Phe, n = 17; 150 μg Phe, n = 3; 200 μg, n = 6.

After a bolus intravenous dose of phenylephrine was given centrally (via the sideport of an Arrow® pulmonary artery catheter introducer sheath), MAP, HR, Doppler signal level, calculated CO, and calculated SVR were recorded every 5 seconds for a total of 2 minutes. Ten minutes after the first trial, after all hemodynamic parameters had returned to baseline, CO was again calibrated using the thermodilution technique and another randomized bolus dose of phenylephrine was administered.

Peak hemodynamic values and time to peak values were analyzed using repeated measures analysis of variance. The effect of patient characteristics on hemodynamic results was examined using the non-parametric Mann-Whitney U test for category data (medical condition, medications, and anesthetics) and repeated measures analysis of variance for continuous data (age, ejection fraction, and baseline hemodynamics). Statistical analysis was controlled for unequal phenylephrine dose group size. When significance was revealed using analysis of variance, the exact P value was determined using unpaired two-tailed t-tests with Bonferroni correction.

Results

General

All patients had significant increases in MAP and calculated SVR, and significant decreases in CO during bolus phenylephrine administration. These results will be examined in detail after an analysis of patient characteristics. There were no ischemic

Table 1. Patient Characteristics

Characteristic	All Patients*
Age, years	63.2 ± 5.6
Medical Condition:	
Ejection Fraction, %	50.8 ± 8.3
Hypertension	14/18
Diabetes	5/18
Myocardial Infarction	11/18
CHF	0/18
Hemodynamics:	
MAP, mm Hg	74.4 ± 7.8
CVP, mm Hg	9.6 ± 3.3
HR, beats·min^{-1}	55.6 ± 18.8
CO, L·min^{-1}	3.9 ± 1.6
SVR, dynes·sec·cm^{-5}	1511 ± 640
Medications:	
Beta-adrenergic blockers	13/18
Calcium channel blockers	12/18
Nitrates	14/18
Anesthetics:	
Ethrane/fentanyl	3/18
Fentanyl	4/18
Isoflurane	9/18
Sufentanil	2/18

*Mean ± SD.

events (premature ventricular contractions, EKG changes, or sustained hemodynamic changes) associated with intravenous phenylephrine administration in any patient. Unless otherwise noted, all results will be presented in terms of phenylephrine dose groups.

Patient Characteristics

Table 1 summarizes patient characteristics including age, medical condition, hemodynamics, medications, and anesthetic drugs. Of note, the mean ejection fraction in this group of patients was 50.8 ± 8.3% (mean ± SD), with a range of 32–63%. The effect of patient characteristics on MAP, SVR, and CO response to intravenous phenylephrine administration will be examined after an analysis of each of these variables alone.

Mean Arterial Blood Pressure Response to Phenylephrine

All patients had significant increases in MAP above baseline levels in response to intravenous bolus phenylephrine (Fig. 1, Table 2). Significant differences between groups ($P < 0.05$) occurred at 115 seconds (50 µg vs. 200 µg phenylephrine). There were no significant differences between groups in
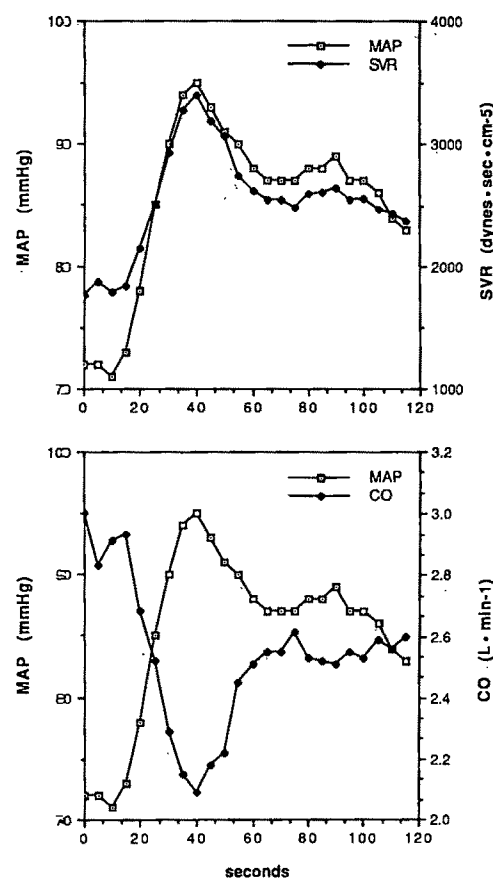

Figure 1. HEMODYNAMIC CHANGES AFTER BOLUS INTRAVENOUS PHENYLEPHRINE ADMINISTRATION. The hemodynamic responses to bolus phenylephrine in a typical patient are presented. Mean arterial blood pressure (MAP) increased, cardiac output (CO) decreased, and systemic vascular resistance (SVR) increased in response to phenylephrine. These peak hemodynamic effects occurred simultaneously approximately 42 seconds after phenylephrine bolus administration.

time to peak MAP. The maximal increase in MAP (+18.0 ± 1.5 mm Hg, mean ± SEM) seen in any phenylephrine dose group occurred in patients receiving 200 µg phenylephrine. Peak MAP occurred in all patients at 41.6 ± 1.4 (mean ± SEM) sec after intravenous phenylephrine injection. There were no significant differences between groups in time to peak change in MAP.

Cardiac Output Response to Phenylephrine

Cardiac output decreased transiently in all patients, concurrent with peak MAP (Fig. 1, Table 2). There were no significant differences in cardiac output between groups at any time interval, but a trend toward a difference was noted between patient groups receiving 50 µg phenylephrine and 200 µg phenylephrine at 25 and 30 seconds. Time to maximal

Table 2. Hemodynamic Changes After Bolus Intravenous Phenylephrine Administration

Seconds	Δ MAP (mm Hg)				Δ SVR (dynes·sec·cm⁻⁵)				Δ CO (L·min⁻¹)			
	Phe 50 μg	Phe 100 μg	Phe 150 μg	Phe 200 μg	Phe 50 μg	Phe 100 μg	Phe 150 μg	Phe 200 μg	Phe 50 μg	Phe 100 μg	Phe 150 μg	Phe 200 μg
0	0	0	0	0	0	0	0	0	0	0	0	0
5	−1.0	−.1	0	0	6	−38	−58	−117	0	.15	.19	.21
	±.2	±.5			±21	±34	±45	±106	±.05	±.17	±.11	±.22
10	−.5	.9	−1.0	.7	29	41	−84	−115	−.09	−.01	.14	.22
	±.5	±1.0	±.6	±1.6	±20	±39	±31	±111	±.04	±.05	±.08	±.59
15	.7	1.2	−1.7	2.3	50*	85	−110	−94	−.09	−.11	.2	.25
	±.6	±1.4	±1.9	±2.7	±23	±70	±18	±125	±.05	±.08	±.11	±.22
20	2.6*	5.6*	1.0	3.7	122*	139	−15	−68	−.17*	−.08	.13	.26
	±1.0	±1.7	±4.6	±3.3	±32	±117	±66	±132	±.07	±.22	±.10	±.22
25	6.6*	9.4*	2.7	5.3	296*	336*	53	−4	−.30*	−.40*	.06	.22
	±1.5	±1.8	±4.3	±3.8	±61	±88	±117	±145	±.10	±.14	±.09	±.23
30	9.7*	12.6*	8.7	9.5*	506*	501*	314	192	−.46*	−.58*	−.12	.04
	±1.8	±1.8	±6.0	±2.8	±93	±78	±290	±150	±.12	±.14	±.24	±.24
35	11.3*	14.4*	11.7	12.5*	647*	601*	645	491*	−.56*	−.68*	−.47	−.29
	±2.0	±2.1	±4.1	±2.4	±113	±97	±364	±176	±.12	±.15	±.25	±.24
40	11.6*	14.6*	14.7*	16.0*	705*	635*	950	826*	−.58*	−.68*	−.73	−.48
	±2.1	±2.2	±2.4	±1.9	±126	±114	±344	±286	±.11	±.13	±.20	±.19
45	11.2*	15.6*	14.3*	17.3*	700*	667*	831	1239*	−.56*	−.63*	−.62*	−.70*
	±2.1	±2.4	±1.2	±1.8	±123	±139	±257	±456	±.11	±.11	±.16	±.14
50	10.9*	15.6*	13.7*	18.0*	766*	685*	768	1490	−.55*	−.60*	−.62*	−.72*
	±1.9	±2.6	±.7	±1.5	±190	±156	±231	±621	±.12	±.12	±.07	±.13
55	10.2*	14.2*	12.7*	16.3*	597*	930*	627	1732	−.48*	−.71*	−.52*	−.77*
	±2.0	±2.8	±1.2	±1.7	±102	±310	±162	±824	±.10	±.18	±.03	±.18
60	8.8*	13.6*	12.0	13.8*	538*	603*	504	1603	−.48*	−.49*	−.37*	−.68*
	±2.0	±2.8	±1.5	±2.2	±93	±167	±128	±856	±.10	±.11	±.03	±.21
65	7.7*	13.8*	11.3	13.0*	490*	613*	472*	1426	−.47*	−.47*	−.38*	−.62
	±2.0	±3.0	±1.9	±2.5	±93	±179	±123	±774	±.10	±.11	±.05	±.25
70	7.0*	13.7*	10.3	13.3*	474*	587*	404	1202	−.40*	−.44*	−.31	−.49
	±2.2	±2.8	±2.0	±2.6	±96	±174	±91	±650	±.07	±.11	±.02	±.23
75	6.5*	13.3*	10.0	11.6*	451*	583*	328	509	−.45*	−.49*	−.16	−.33
	±2.1	±2.7	±2.1	±2.6	±93	±169	±90	±211	±.10	±.11	±.04	±.17
80	7.9*	13.1*	9.3	13.6*	478*	549*	314	415*	−.45*	−.41*	−.19*	−.13
	±2.0	±2.8	±2.0	±2.4	±88	±175	±91	±131	±.10	±.11	±.02	±.18
85	7.4*	13.2*	9.3	14.5*	439*	591*	311	837	−.41*	−.44*	−.17*	−.42*
	±2.0	±2.8	±2.0	±2.2	±79	±177	±80	±356	±.11	±.10	±.03	±.16
90	8.0*	12.9*	8.7	14.8*	456*	639*	286	745	−.42*	−.47*	−.13	−.33
	±1.9	±3.1	±1.8	±2.4	±75	±196	±78	±315	±.12	±.14	±.07	±.15
95	6.3*	14.6*	8.0	13.7*	386*	694*	324	756*	−.40*	−.48*	−.24*	−.44*
	±1.8	±3.3	±1.5	±2.6	±72	±203	±91	±271	±.11	±.13	±.03	±.12
100	5.7*	12.9*	7.0	13.3*	338*	595*	377	641	−.38*	−.46*	−.32	−.27
	±1.9	±3.1	±2.5	±2.2	±73	±189	±159	±275	±.12	±.14	±.10	±.14
105	5.2*	12.4*	6.3	13.5*	318*	576*	376	587	−.36*	−.42*	−.27	−.23
	±1.8	±2.9	±4.5	±2.6	±69	±192	±214	±255	±.12	±.14	±.20	±.22
110	4.7	11.4*	6.3	14.2*	314*	529*	319	529*	−.34*	−.36*	.−17	−.14
	±1.8	±2.8	±4.9	±3.0	±69	±174	±238	±205	±.12	±.13	±.22	±.16
115	3.8	9.6*	6.0	14.3*	287*	355*	510	567*	−.37*	−.33*	−.27	−.22
	±1.7	±2.6	±4.6	±3.3	±60	±104	±487	±209	±.13	±.12	±.46	±.12

Mean ± SEM, *significant at the 95% confidence level from baseline.
Groups: 50 μg Phe, N = 14; 100 μg Phe, N = 12; 150 μg Phe, N = 3; 200 μg Phe, N = 5.
Abbreviations: Phe = phenylephrine, MAP = mean arterial pressure, SVR = systemic vascular resistance, CO = cardiac output, μg = micrograms.

decrease in cardiac output occurred at 42.5 ± 1.7 (mean ± SEM) seconds after phenylephrine injection in all patients; no significant differences were noted between groups in time to maximal decrease in cardiac output. The maximal decrease in cardiac output seen in any patient group (−0.77 ± 0.18 L·min⁻¹, mean ± SEM) occurred in patients receiving 200 μg phenylephrine.
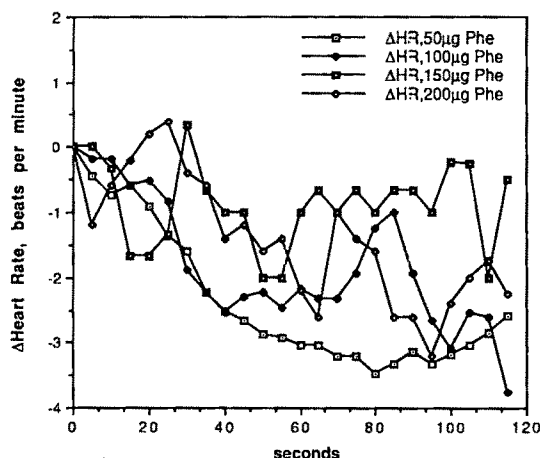
Figure 2. CHANGE IN HEART RATE AFTER BOLUS PHENYL-EPHRINE ADMINISTRATION. Heart rate (HR) decreased in all patients with the administration of bolus phenylephrine (Phe). These decreases were significant ($P < 0.05$) only in patients receiving 50 μg and 100 μg phenylephrine. Maximal decrease in heart rate occurred at approximately 49 seconds post phenylephrine, significantly ($P < 0.05$) later than other hemodynamic parameters. μg = micrograms.

Systemic Vascular Resistance Response to Phenylephrine

Calculated systemic vascular resistance increased in all patients given bolus phenylephrine (Fig. 1, Table 2). Peak SVR occurred concurrently with peak MAP. There were no significant differences in SVR between groups at any time period, but a trend toward a difference was noted between patient groups receiving 50 μg phenylephrine and 200 μg phenylephrine at 50 and 55 seconds. The maximal increase in SVR ($+1732 \pm 824$ dynes·sec·cm^{-5}, mean $\pm$ SEM) seen in any patient group occurred in patients given 200 μg phenylephrine. Time to peak SVR occurred at 41.2 ± 1.4 (mean $\pm$ SEM) seconds after phenylephrine injection in all patients; no significant differences were noted between groups in times to peak SVR.

Heart Rate Response to Phenylephrine

Heart rate decreased in all patients with the administration of bolus phenylephrine (Fig. 2). Heart rate decreases were significant ($P < 0.05$) in patients receiving 50 μg and 100 μg phenylephrine, but did not reach significance in the patients given 150 μg and 200 μg phenylephrine. Maximal decrease in heart rate occurred at 49.0 ± 3.4 (mean $\pm$ SEM) seconds in all patients, significantly ($P < 0.05$) later than either time to peak MAP or time to peak SVR.

Effect of Patient Characteristics on Hemodynamic Responses to Phenylephrine

The effects of patient characteristics on peak change in MAP, cardiac output, and SVR were evaluated for each phenylephrine dose level. The presence of hypertension was associated with changes in MAP, SVR, and CO that were significantly smaller than in patients without hypertension in the lowest phenylephrine dose range. Age was negatively correlated with peak SVR in patients given 50 μg phenylephrine. Hence, older patients had less increase in SVR than younger patients. There was a positive correlation between ejection fraction and peak MAP and SVR in patients given 100 μg phenylephrine. Hence, the lower the ejection fraction, the less the increase in MAP and SVR in these patients. Baseline cardiac output was negatively correlated with the change in cardiac output. In other words, patients with low baseline cardiac outputs decreased their cardiac outputs further in response to phenylephrine than did patients with higher baseline cardiac outputs. And finally, patients with a high SVR at baseline increased their SVR and decreased their CO more after phenylephrine than did patients with lower baseline SVR.

Effect of Anesthetic Agent on Peak Hemodynamic Values

The effect of anesthetic agent on peak hemodynamic effect after bolus phenylephrine administration was also analyzed. Isoflurane and sufentanil had no effect on peak hemodynamic values. High dose fentanyl anesthesia (>50 μg/kg) correlated positively with ΔMAP at 50 μg phenylephrine and with ΔSVR at 100 μg phenylephrine. Hence patients receiving high dose fentanyl increased MAP and SVR significantly more than patients receiving other anesthetics. Likewise, the combination of low dose fentanyl (<25 μg/kg) and ethrane was associated with higher peak ΔMAP and ΔSVR in patients receiving 50 μg and 100 μg phenylephrine. There were not enough patients in groups given 150 and 200 μg phenylephrine to analyze for the effect of anesthetic agent.

Discussion

General

In summary, phenylephrine intravenous bolus administration increases MAP, decreases CO, and in-

creases calculated SVR in patients with ischemic heart disease. Why is it important to understand the beat-to-beat hemodynamic effects of phenylephrine? The answer to this question is two-fold. First, it has been postulated that in patients with ischemic heart disease, bolus phenylephrine administration may be accompanied by a rapid increase in SVR followed by a decrease in CO, with potentially little or no blood pressure change. Every patient in our study had a significant increase in mean arterial blood pressure with the administration of phenylephrine in spite of the presence of known ischemic heart disease and decreases in cardiac output. This disproves the null hypothesis that no change in MAP would be seen in patients with myocardial disease. This is important clinically since it implies that in patients with myocardial disease, a decrease in CO will be accompanied by a simultaneous increase in blood pressure when phenylephrine is administered.

Secondly, in studies on alpha-adrenergic responsiveness using a bolus phenylephrine technique, it is imperative to understand the timing of measureable events such as blood pressure, CO, and calculated SVR. This study describes for the first time the dynamic characteristics of alpha-1-adrenergic stimulation with phenylephrine bolus administration. Peak MAP, peak SVR, and trough CO occurred simultaneously at approximately 42 seconds after administration of bolus phenylephrine.

Esophageal Doppler Method for Measuring Cardiac Output

The method of measuring CO using esophageal Doppler has been validated in several studies (7,9–12). It was chosen in this study because it provided an easy, clinically applicable technique for continuously measuring CO as compared to the intermittant thermodilution method. This is especially important when bolus doses of pressors such as phenylephrine are used, since several seconds are required to measure cardiac output using the thermodilution method. Also it is impossible to predict when the peak blood pressure effect of an alpha–adrenergic agonist will occur, making simultaneous measurement of peak MAP and CO almost impossible using thermodilution methods. However, some investigators question the use of esophageal Doppler for measuring CO (13,14) particularly in studies where pressors are used since increased blood pressure may increase the diameter of the descending aorta (14). Theoretically, if aortic diameter increases, blood velocity in the descending aorta would decrease causing a decreased

Doppler shift and an artificially decreased cardiac output (and hence larger ΔCO). A recent study (14) done on sheep, using pizoelectric crystals to continuously measure aortic diameter, showed that over the range of MAP between 40 mm Hg and 175 mm Hg the relationship between thermodilution cardiac output (TD) and esophageal Doppler cardiac output (DE) could be expressed by the equation TD/DE = 0.466 + 0.005 MAP. Using this equation, esophageal Doppler will only underestimate thermodilution cardiac output once MAP increases above 106.8 mm Hg. None of the patients in our study had blood pressures this high, and so this theoretical problem in study design was not realized clinically.

Heart Rate Response to Phenylephrine

Heart rate decreased significantly in patients receiving phenylephrine. While this study was not designed to assess baroreflex responses to phenylephrine, this finding supports the classic baroreflex response to phenylephrine reported in several studies (15–17). Since HR was included in determination of CO by the equation: CO = (HR)·(Doppler Signal Level)·(Constant), changes in HR were reflected in changes in both CO and SVR values. Hence, HR was not a confounding factor in this study.

Effect of Patient Characteristics on Hemodynamic Responses to Phenylephrine

Several effects of patient characteristics on hemodynamic responses to phenylephrine were observed in this study. It is important to note here that stringent statistical analysis criteria were used in evaluating this question in order to avoid Type I errors (rejecting the null hypothesis [i.e., finding a significant effect of patient characteristics on hemodynamic responses] when the null hypothesis is true [i.e., when no effect of patient characteristics actually exists]). As a result, only certain phenylephrine dosage levels were found to be statistically significant with regard to patient characteristics. More patients (larger n) would be required to determine if these associations occur over all dose ranges studied.

The presence of hypertension was associated with changes in MAP, SVR, and CO that were smaller than in patients without hypertension in the lowest phenylephrine dose range. Since one explanation of the vascular response to chronic hypertension is the presence of volume contraction, elevated plasma catecholamine levels, and increased tonic contraction of

the vasculature (18–20), this result is not surprising. It can be postulated that previously contracted peripheral vessels may be only able to contract a smaller amount than previously uncontracted vessels. A smaller change in afterload in hypertensive patients may also result in smaller decreases in CO. Our results support this hypothesis.

Age was negatively correlated with peak SVR in patients given 50 μg phenylephrine; that is, elderly patients had less increase in SVR than did younger patients. Since age has been associated with progressive reductions in vascular distensibility, chronically elevated plasma levels of catecholamines, and potentially decreased vascular responsiveness (21–26), this may account for the smaller increase in SVR in response to phenylephrine in elderly patients seen in this study. Of note, baseline SVR was not significantly influenced by age in our patient population.

Two measures of cardiac function, EF and CO, had similar effects on hemodynamic responses to phenylephrine. A positive correlation was present between EF on the one hand and MAP and SVR on the other hand in patients given 100 μg phenylephrine. Hence, the lower the EF, the less the increase in MAP and SVR seen in response to IV phenylephrine in these patients. There is evidence that anesthetized patients with poor ventricular function have impaired alpha-1-adrenergic responsiveness (27); this could account for the results seen in this study. In addition, baseline CO was negatively correlated with change in cardiac output; in other words, patients with low baseline CO decreased their CO further in response to phenylephrine than did patients with higher baseline CO. This seems intuitively obvious. Patients with poor ventricular function are least able to cope with increases in afterload presented to the left ventricle. In spite of this finding, patients with low baseline CO did increase MAP in response to phenylephrine. This may be important clinically in the setting of hypotension where phenylephrine may be used to increase blood pressure acutely in patients with low CO before more definitive methods of increasing CO are instituted for ultimate correction of the hypotension.

Patients with high baseline SVR increased SVR and decreased their CO further after phenylephrine more than did patients with lower baseline SVR levels. At first this finding appears to contradict the results seen in the hypertensive and elderly patients. However, chronically elevated plasma levels of catecholamines are present in patients with hypertension and in the elderly (18,19,22) and this may possibly lead to vascular hyporesponsiveness. However, patients who are young and not hypertensive can be anxious prior to surgery and this can lead to acutely

increased baseline SVR levels. Such patients may require less phenylephrine to further increase their SVR as is seen in this group of patients in our study, although this can be determined only with further studies.

Effect of Anesthetic Agent on Peak Hemodynamic Values

Both high dose fentanyl (>50 μg·kg^{-1}) and low dose fentanyl (<25 μg·kg^{-1}) combined with enflurane were associated with significantly larger ΔMAP and ΔSVR than other anesthetic agents. This suggests that fentanyl interferes less with phenylephrine agonism at the α_1-adrenergic receptor than the other anesthetic agents used. Since this study was not designed to look specifically at anesthetic agent effects on α_1-adrenergic responsiveness, the number of patients in each anesthetic group was small. This, combined with the lack of a control (unanesthetized group) and knowledge that isoflurane vasodilation is not mediated via the α_1-adrenergic receptor (29), prevents further speculation about the effect of anesthetics on the hemodynamic responses to phenylephrine from this study.

In conclusion, this study describes for the first time the dynamic characteristics of alpha-1-adrenergic stimulation with phenylephrine bolus administration in patients with myocardial disease. Phenylephrine intravenous bolus administration increases mean arterial blood pressure, decreases cardiac output, and increases calculated systemic vascular resistance in patients with ischemic heart disease; these peak hemodynamic effects occur simultaneously approximately 42 seconds after phenylephrine administration. This is important clinically since it shows that in spite of a transient decrease in cardiac output, phenylephrine bolus administration is accompanied by a simultaneous rise in blood pressure in patients with myocardial disease.

References

1. Ruffolo RR. Interaction of agonists with peripheral α-adrenergic receptors. FASEB J 1984;43:2910–6.

2. Starke K, Docherty JR. Alpha$_1$- and alpha$_2$-adrenoceptors: pharmacology and clinical implications. J Cardiovasc Pharmacol 1981;3:S14–23.

3. Woodman OL, Vatner SF. Cardiovascular responses to the stimulation of alpha-1 and alpha-2 adrenoceptors in the conscious dog. J Pharmacol Exp Ther 1986;237:86–91.

4. Gasic S, Eichler HG, Korn A. Effect of ketanserin on phenylephrine-dependent changes in splanchnic hemodynamics and systemic blood pressure in healthy subjects. J Cardiovasc Pharmacol 1985;7:219–23.

5. Ekenvall L, Lindblad LE. Is vibration white finger a primary sympathetic nerve injury? Br J Ind Med 1986;43:702–6.

6. Ahlquist RP. Present state of alpha- and beta-adrenergic drugs. I. The adrenergic receptor. Am Heart J 1976;92:661–4.

7. Mark JB, Steinbrook RA, Gugina LD, Maddi R, Hartwell B, Shemin R, DiSesa V, Rida WN. Continuous noninvasive monitoring of cardiac output with esophageal Doppler ultrasound during cardiac surgery. Anesth Analg 1986;65:1013–20.

8. Roewer N, Bednarz F, Schulte AM, Esch J. Continuous measurement of intracardiac and pulmonary blood flow velocities with transesophageal pulsed Doppler echocardiography: technique and initial clinical experience. J Cardiothor Anesth 1987;1:418–28.

9. Freund PR, Padavich CA. A comparison of cardiac output techniques: transesophageal Doppler versus thermodilution cardiac output during general anesthesia in man. Anesthesiology 1985;63:A191.

10. Wong DH, Tremper KK, O'Connor D, Wilbur S, Wakabayashi A, Zaqccari J. Non-invasive cardiac output: comparison of two different methods with thermodilution. Anesthesiology 1987;67:A643.

11. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984;70:425–31.

12. Thys DM, Hillel Z, Estioko E. Left-ventricular contractility can be determined by continuous esophageal Doppler. Anesthesiology 1987;67:A77.

13. Siegel LC, Shafer SL, Martinez GM, Ream AK, Scott JC. Comparison of simultaneous intraoperative measurements of cardiac output by thermodilution, esophageal Doppler and electrical impedance in anesthetized patients. Anesthesiology 1987;67:A181.

14. List W, Gravenstein N, Banner T, Caton D, Davis RF. Interaction in sheep between mean arterial pressure and cross-sectional area of the descending aorta: implications for esophageal Doppler monitoring. Anesthesiology 1987;67:A178.

15. Greenway CV, Innes IR. Effect of carotid sinus baroreceptor reflex on responses to phenylephrine and nitroprusside in anesthetized cats. J Cardiovasc Pharmacol 1981;3:169–77.

16. Mancia G, Bonazzi O, Pozzoni L, Ferrari A, Gardumi M, Gregorini L, Perodi R. Baroreceptor control of atrioventricular conduction in man. Circ Res 1979;44:752–8.

17. Goldman WF, Saum WR. A direct excitatory action of catecholamines on rat aortic baroreceptors in vitro. Circ Res 1984;55:18–30.

18. Buhler FR, Amann FW, Bolli P, Hulthen L, Kiowski W, Landmann R, Burgisser E. Elevated adrenaline and increased α-adrenoceptor-mediated vasoconstriction in essential hypertension. J Cardiovasc Pharmacol 1982;4:S134–S138.

19. Goldstein DS. Arterial baroreflex sensitivity, plasma catecholamines, and pressor responsiveness in essential hypertension. Circulation 1983;2:234–40.

20. Laragh JH. Two forms of vasoconstriction in systemic hypertension. Am J Cardiol 1987;60:82G–93G.

21. Fleg JL. Alterations in cardiovascular structure and function with advancing age. Am J Cardiol 1986;57:33C–44C.

22. Messerli FH, Ventura HO, Glade LB, Sundgaard-Rhse K, Duna F, Frohlich E. Essential hypertension in the elderly; hemodynamics, intravascular volume, plasma renin activity and circulating catecholamine levels. Lancet 1983;244:H513–H518.

23. Palmer GJ, Ziegler MG, Lake CR. Response of norepinephrine and blood pressure to stress increases with age. J Gerontol 1978;33:482–7.

24. Rowe JW. Clinical consequences of age-related impairments in vascular compliance. Am J Cardiol 1987;60:68G–71G.

25. Higginbotham MB, Morris KG, Williams RS, Coleman RE, Cobb FR. Physiologic basis for the age-related decline in aerobic work capacity. Am J Cardiol 1986;57:1374–9.

26. Elliott HL, Sumner DJ, McLean K, Reid JL. Effect of age on the responsiveness of vascular alpha-adrenoceptors in man. J Cardiovasc Pharmacol 1982;4:388–92.

27. Schwinn DA, McIntyre RW, Hawkins ED, Kates RA, Reves JG. α-adrenergic responsiveness during CABG: effect of preoperative ejection fraction. Anesthesiology 1988;69:206–17.

28. Schwinn DA, McIntyre RW, Reves JG. Effect of isoflurane anesthesia on alpha-1-adrenergic responsiveness in patients undergoing coronary artery bypass graft surgery. Anesthesiology, 1988;69:A137.

Effects of Cholestatic Hepatic Disease and Chronic Renal Failure on Alfentanil Pharmacokinetics in Children

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DAVIS PJ, STILLER RL, COOK DR, BRANDOM BW, DAVIS JE, SCIERKA AM. Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. Anesth Analg 1989;68:579-83.

The role of the liver and the kidney in alfentanil metabolism has not been defined. The effects of cholestatic hepatic disease and chronic renal failure on the pharmacokinetics of alfentanil were evaluated in 9 children undergoing liver transplantation and 10 children undergoing kidney transplantation. These findings were compared with data from 10 children with normal hepatic and renal function undergoing other surgical procedures. There was no statistical difference among the 3 groups with respect to apparent volume of distribution, half-life, or clearance. In a subgroup of 3 patients undergoing liver transplantation alfentanil kinetics were determined both before and after the allograft was incorporated into the recipient's circulation. Though both volume of distribution and elimination half-life increased in the posttransplantation period, only the decrease in clearance was statistically significant. Thus, it appears that alfentanil may be a useful anesthetic agent in pediatric patients with cholestatic hepatic disease or chronic renal failure. The dose of alfentanil in these patients need not be altered except in the period immediately after liver transplantation.

Key Words: ANESTHESIA—pediatrics. ANESTHETICS, INTRAVENOUS—alfentanil. PHARMACOKINETICS—alfentanil. KIDNEY, RENAL FAILURE—alfentanil. LIVER, HEPATIC FAILURE—alfentanil.

In addition to the effects of age, disease processes can greatly influence the disposition and elimination of opioid compounds. Alfentanil undergoes N-dealkylation and is eliminated almost exclusively by the liver. Approximately 1% of the drug appears unchanged in the urine (1–3). The pharmacokinetics of alfentanil have been shown to differ markedly in adult surgical patients with alcoholic hepatic disease or renal insufficiency compared with control patients (1,4). At present, there are no published reports of alfentanil pharmacokinetics in children with hepatic or renal failure. However, in healthy children undergoing routine surgery, alfentanil has been reported to have a small volume of distribution, short elimination

half-life, and stable cardiovascular properties (5–7). These pharmacologic attributes make alfentanil a potentially useful anesthetic in pediatric patients with either hepatic or renal disease. This study was designed to evaluate the pharmacokinetics of alfentanil in pediatric patients undergoing hepatic or renal transplantation.

Methods

With the approval of the institutional review board and the informed written consent of a parent, 29 patients were studied in three groups. Group 1 consisted of 9 patients with cholestatic hepatic disease (7 with biliary atresia, 1 with α_1-antitrypsin deficiency, and 1 with Wilson's disease). They ranged in age from 9 months to 15 years (mean $\pm$ SD, 4.6 $\pm$ 4.5 years) and were scheduled to undergo orthotopic liver transplantation. Table 1 summarizes the clinical features of these patients. Group 2 comprised 10 children with endstage renal disease requiring either peritoneal dialysis or hemodialysis sched-

Table 1. Clinical Characteristics of Patients With Liver Disease

Age (years)	Diagnosis[a]	SGPT IU	AlkØ IU	Bili (t/d)[b] (mg/dL)	Albumin (g/dL)	PT[c] (%)
3	BA	139	70	32.4/23.6	3.8	116
2.5	BA	163	1245	1.5/0.8	3.9	116
5	BA	138	1270	32/18	3.6	116
1.5	BA	84	750	16.2/10.7	3.3	108
7	BA	197	514	9.6/7.6	3.5	116
0.75	BA	78	—	21/18	2.8	133
0.75	BA	137	589	47/42	3.5	141
6	AD	126	465	1/0.3	3.7	118
15	WD	188	56	37/34	2.0	166

[a]BA, biliary atresia; AD, α_1-antitrypsin deficiency; WD, Wilson's disease.
[b]Bilirubin (total/direct).
[c]PT, prothrombin time, expressed as percent of control.

uled to undergo kidney transplantation. Their mean age was 12.6 ± 3.2 years. The mean blood urea nitrogen and creatinine levels in these patients were 72 ± 22 and 9.4 ± 3.3 mg/dL respectively. Group 3 included 10 children aged 9 months to 10 years (mean ± SD, 5.0 ± 2.8 years) who required invasive monitoring for surgical procedures. They had no evidence of hepatic or renal disease.

In all groups, anesthesia was induced with nitrous oxide, oxygen, and halothane. After an intravenous catheter had been inserted, halothane was discontinued and fentanyl or sufentanil and pancuronium were administered. An arterial catheter was then inserted. Alfentanil (25–100 μg/kg) was administered over 30 sec into a peripheral vein. Arterial blood samples were obtained at 1, 2, 3, 5, 7.5, 10, 12, 15, 20, 30, 45, 60, 90, and 120 min after injection. The sampling period was truncated at 120 minutes because at that time liver transplant patients begin to have blood loss approaching 10% of the calculated blood volume. Any patient whose blood loss exceeded 10% of the blood volume before 120 minutes was excluded from the study. In 3 of the 9 patients undergoing liver transplantation, after the transplanted liver had been reperfused and cardiovascular stability and hemostasis achieved, a second dose of alfentanil identical to the first was administered intravenously over 30 sec. Arterial blood samples for alfentanil determination were obtained just before the injection (T0) and at 1, 2, 3, 5, 7.5, 10, 12, 15, 20, 30, 45, 60, 90, and 120 min after the infusion. In all 3 patients, this second injection was at least 12–24 hours after the first and 8–12 hours after reperfusion of the grafted liver.

In the patients undergoing kidney transplantation arterial blood samples were collected until incorporation of the transplanted kidney into the donor circulation. In an effort to compare kinetic parameters determined during analogous time periods, we re-

port values obtained from samples taken 120 min after the injection of alfentanil.

Blood samples were immediately separated, and the plasma was stored at −60°C. All samples were measured in duplicate. Alfentanil concentrations were determined with a specific radioimmunoassay (8). This assay accurately detects 0.1 ng/kg of alfentanil with interassay and intraassay coefficients of variation of 4% and 3%, respectively. It was verified that antibodies directed to alfentanil failed to bind fentanyl or sufentanil to any extent.

The pharmacokinetic data were analyzed with a model-dependent computation using a Niazi program with a logarithm non-linear regression analysis (9). The decay curve for alfentanil concentration from time 0 to 120 minutes was evaluated. This curvilinear form was best described by a biexponential equation, and the goodness of fit was obtained from the coefficient of determination. In all patients, the weighted sum of the squares was not sufficiently reduced by the addition of a third compartment. The pharmacokinetic parameters were determined by standard formulas. The area under the concentration-time curve (AUC) was calculated using the trapezoidal rule from $t = 0$ to $t = 120$ and from $t = 0$ to ∞; clearance (Cl) as $Cl_{120} = dose/AUC_{120}$; apparent volume of distribution (Vd_{120}) as $Vd_{120} = dose/\beta(A/\alpha + B/\beta)$; distribution half-life ($t_{1/2\alpha}$) as $t_{1/2\alpha} = 0.693/\alpha$; and elimination half-life ($t_{1/2\beta}$) as $t_{1/2\beta} = 0.693/\beta$. A one-way analysis of variance was performed to determine the statistical significance of differences among the 3 groups, and a Student t-test was performed to determine statistical significance between the before and after hepatic transplantation periods (10). Statistical significance was assumed for $P < 0.05$.

Results

For all 3 groups the plasma concentration curve could best be described by a biexponential equation, with

Table 2. Pharmacokinetics of Alfentanil in Children With Hepatic Disease (Group 1), Children With Chronic Renal Failure (Group 2), and Normal Control Patients (Group 3)[a]

	$t_{1/2\alpha}$ (min)	$t_{1/2\beta_{120}}$ (min)	Cl_{120} (mL/ kg/min)	Vd_{120} (L/kg)
Group 1	2.7 ± 1.0	45.8 ± 13.3	7.59 ± 3.6	0.46 ± 0.16
Group 2	3.4 ± 1.7	41.5 ± 11	8.2 ± 4.4	0.45 ± 0.10
Group 3	3.3 ± 2.5	41.6 ± 16	7.25 ± 4.3	0.40 ± 0.21

[a]Mean $\pm$ SD.

the goodness of fit for the curves being 0.97 ± 0.03. The ratio of the area under the concentration time curve at 120 minutes and infinity (AUC_{120}/AUC_∞) was 0.84 ± 0.08 for the hepatic disease pre-transplant patients, 0.71 ± 0.17 for the post-transplant patients, 0.90 ± 0.07 for the renal failure patients and 0.90 ± 0.05 for the control patients. Table 2 summarizes the pharmacokinetic data. There was no statistically significant difference in clearance, apparent volume of distribution, or half-life among the 3 groups.

In the 3 patients (Table 3) undergoing liver transplantation (Group 3) in whom kinetics were determined before and after transplantation, the plasma concentration of alfentanil at T_0 prior to the post-transplantation injection was less than the sensitivity of the assay. Though increases in apparent volume of distribution (0.47 ± 0.23 L/kg vs 0.83 ± 0.55 L/kg) and terminal elimination half-life (41 ± 19 min vs 82 ± 38 min) were observed in these patients, only the decrease in clearance (11.2 ± 2.7 mL·kg^{-1}·min^{-1} vs 7.0 ± 3.8 mL·kg^{-1}·min^{-1}) was statistically significant.

Discussion

Though the liver is the major site of drug biotransformation, the effects of hepatic dysfunction on drug elimination and disposition are inconsistent (11). The degree of liver dysfunction as well as a drug's ability to bind to plasma proteins are important variables in determining drug kinetics in patients with liver disease. For drugs with a high hepatic extraction ratio, hepatic clearance is sensitive to changes in hepatic blood flow; while for drugs with a low hepatic extraction ratio, hepatic drug clearance becomes a function of intrinsic hepatic enzyme activity and protein binding (11). Thus, the reported inconsistent effect of liver disease on drug pharmacology may be a function of the heterogeneous pathophysiology of liver disease with respect to hepatocellular function, protein binding, and hepatic blood flow. For hepatic diseases that preserve hepatic blood flow but impair hepatocellular

function, the pharmacokinetic profile of a drug with a high hepatic extraction ratio will be relatively unaffected. But for a drug with a low hepatic extraction ratio, similar hepatic pathophysiologic impairment would result in a pronounced alteration in the drug's disposition and elimination.

The effects of liver disease on the disposition and elimination of narcotics have been studied in adults. Habener et al. (12) studied fentanyl pharmacokinetics in adult surgical patients with cirrhosis. They noted that fentanyl had a high hepatic extraction ratio and its kinetics were unaffected by cirrhosis. Whether this lack of effect was a function of the patient's underlying hepatic disease and relative preservation of hepatic blood flow or alternatively a function of fentanyl's characteristic large peripheral compartment and small central compartment (which make little drug available for hepatic clearance) is unclear.

Patwardhan et al. (13) have described the effects of liver disease on morphine kinetics in both nonsurgical cirrhotic patients and normal volunteers. Compared with normal subjects, patients with moderate to severe cirrhosis had a normal elimination and disposition of morphine but a prolonged elimination half-life and decreased clearance of indocyanine. Since morphine is a highly extracted drug and its clearance depends on hepatic blood flow, the authors postulated that morphine has extrahepatic sites of metabolism in the gastrointestinal tract and kidney. In a report of 2 children undergoing liver transplantation Shelly et al. (14) noted that morphine was metabolized rapidly. One of these patients had impaired renal function, and morphine metabolites (morphine 3-glucuronide and morphine 6-glucuronide) were noted to accumulate. The accumulation of these metabolites was associated with prolonged narcosis.

The effects of alcoholic cirrhosis on alfentanil metabolism in adult surgical patients have been described by Ferrier et al. (1). Compared with control patients, cirrhotic patients demonstrated a similar apparent volume of distribution but significantly lower plasma clearance (1.6 ± 1.0 mL·kg^{-1}·min^{-1} vs 3.1 ± 1.6 mL·kg^{-1}·min^{-1}) and longer elimination half-life (90 ± 18 min vs 219 ± 128 min). In addition, the protein binding was less in cirrhotic patients than in the control group. When the kinetic parameters were corrected for protein binding, the unbound volume of distribution and the free drug clearance were decreased in the patients with cirrhosis. Our findings contrast with those reported by Ferrier et al. (1). Though we did not measure protein binding and therefore cannot comment on the pharmacokinetics of the unbound fraction, we note that in children, the

Table 3. Pharmacokinetics of Alfentanil in Three Patients Before and After Liver Transplantation[a]

	$t_{1/2\alpha}$ (min)	$t_{1/2\beta_{120}}$ (min)	Cl_{120} (mL/kg/min)	Vd_{120} (L/kg)
Before transplantation	2.9 ± 0.63	41 ± 19	11.2 ± 2.7	0.47 ± 0.23
After transplantation	4.3 ± 0.95	82 ± 38	7.0 ± 3.8*	0.83 ± 0.55

[a]Mean ± SD.
*$P < 0.05$ compared with value before transplantation.

overall pharmacokinetic profile of alfentanil was unaffected by cholestatic liver disease. Differences in our results and those of Ferrier et al. (1) may be related to the age of the patients, differences in the length of plasma sampling times (2 vs 10 hours) and/or to the differences in the underlying pathophysiology of the respective liver diseases, i.e., hepatocellular dysfunction (alcoholic cirrhosis) and cholestatic liver disease.

Studies have shown that hepatic blood flow is quite variable in adult patients with acute or chronic liver disease (15). In addition, liver disease can alter protein binding either by changing binding concentration or protein configuration or by producing protein binding inhibitors (11,15,16). Since alfentanil is a drug of intermediate hepatic extraction (17,18), changes in blood flow, protein binding, and intrinsic liver activity are all factors that can affect its pharmacokinetic profile. Thus, to explain the observed pharmacokinetic variability, both between individuals with identical hepatic disease and within individuals over time, will require a better understanding of the pathophysiologic basis of liver disease.

In a small subgroup of patients we determined alfentanil kinetics before and after replacement of the diseased liver. In an effort to compare kinetic parameters obtained during an analogous interval, we report the posttransplantation values from samples obtained until 120 minutes after the second injection. Though all the kinetic parameters changed after incorporation of the donor liver into the recipient's circulation, only the decrease in plasma clearance was significant. Whether this observed decrease in clearance in a limited number of patients is an indicator of incomplete allograft function, a consequence of injury during organ procurement and preservation, or an effect of massive blood transfusion and altered protein binding is unclear and will therefore require further evaluation.

The pharmacokinetic profile of narcotics also may be altered in renal disease (19–21). Because of the pathophysiologic changes associated with renal failure, patients with chronic renal failure frequently have alterations in protein binding, in the volumes in which drugs distribute, and in the clearance rates in which drugs are eliminated. Chauvin and others have studied the pharmacokinetics of alfentanil and

morphine in adult patients with renal insufficiency (19,20). For morphine, they found that patients with chronic renal failure had similar rates of clearance and half-lives but significantly smaller steady-state volumes of distribution, compared with age- and weight-matched control patients. Although chronic renal failure did not alter the elimination of unchanged morphine, metabolites of morphine accumulated at higher plasma levels and for longer time periods in the patients with chronic renal failure.

As with morphine, the pharmacokinetics of alfentanil in adults with renal failure demonstrated similar clearance and half-life but larger steady-state volume of distribution compared with the values in normal control patients. When the kinetic parameters of alfentanil were corrected for protein binding, the volume of distribution and clearance rate for the unbound drug were similar in the 2 groups (20). Little information is available on the pharmacokinetics of opioids in children with renal failure. In a study of sufentanil kinetics in adolescent patients undergoing kidney transplantation, Davis et al. (21) reported no statistical significance with regard to differences in clearance, elimination half-life, or volume of distribution in patients with normal versus abnormal renal function, though the kinetics in patients with chronic renal failure did demonstrate a wide variability. Similarily the present study suggests that renal disease does not affect the pharmacologic profile of alfentanil in children. These findings contrast with the findings in adults with renal failure reported by Chauvin et al. (20).

We acknowledge that the length of our sampling time may have affected the calculated pharmacokinetic parameters of alfentanil. Unfortunately, the sampling time was limited by the constraints of the surgical procedure. In the liver transplant patients we elected to end the sampling period when the patients' blood loss approached 10% of the estimated blood volume. In the kidney transplant group we speculated that both the absence of renal function and the revascularization of the transplanted kidney would influence the kinetics of alfentanil. We therefore limited sampling to the anephric period. In an attempt to compare kinetic parameters among the 3 groups, analogous time intervals were chosen, and

the pharmacokinetic data were obtained from samples taken during the first 120 minutes postinjection. Although for the 3 groups the area under the concentration time curve at 120 minutes (AUC_{120}) represents 84–90% of the area under the extrapolated curve of concentration vs the time at infinity (AUC_∞), it must be noted that all our pharmacokinetic calculations, though descriptive of the clinical situation, may not truly represent the drug's terminal disposition profile. For this reason we have characterized these pharmacokinetic estimates with a sampling-time subscript (e.g., Vd_{120}).

Cholestatic hepatic disease and chronic renal failure with underlying alterations in fluid and electrolyte homeostasis, disturbances in regional blood flow, and changes in organ function, do not appear to alter the disposition and elimination of alfentanil in children. Thus, in these children, alfentanil may be a useful anesthetic agent and its dosage need not be altered. In patients immediately after liver transplantation, however, alfentanil clearance appears to be altered. Whether the observed pharmacokinetic changes are a consequence of incomplete allograft function or of massive blood transfusion is yet unclear.

References

1. Ferrier C, Marty J, Bouffard MD, Haberer JP, Levron JC, Duvaldestin MD. Alfentanil pharmacokinetics in patients with cirrhosis. Anesthesiology 1985;62:480–4.

2. Stanski DR, Hug CC. Alfentanil—a kinetically predictable narcotic analgesic. Anesthesiology 1982;57:435–8.

3. Schuttler J, Stoeckel H. Alfentanil (R 39209): Ein neues kurzwirkindes opioid. Anaesthesist 1982;31:10–4.

4. Chauvin M, Lebrault C, Levron JC, Duvaldestin P. Pharmacokinetics of alfentanil in chronic renal failure. Anesthesiology 1987;66:53–6.

5. Goresky GV, Koren G, Sabourin MA, Sale JP, Strunin L. The pharmacokinetics of alfentanil in children. Anesthesiology 1987;67:654–9.

6. Meistelman C, Saint-Maurice C, Lepaul M, Levron J, Loose J, MacGee K. A comparison of alfentanil pharmacokinetics in children and adults. Anesthesiology 1987;66:13–6.

7. Roure P, Jean N, Leclerc A-C, Cabanel N, Levron J-C, Duvaldestin P. Pharmacokinetics of alfentanil in children undergoing surgery. Br J Anaesth 1987;59:1437–40.

8. Michiels M, Hendricks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Pharmacokinetic profile in man. J Pharm Pharmacol 1983;35:86–93.

9. Niazi S. Application of a programmable calculator in data fitting according to one and two-compartment open models in clinical pharmacokinetics. Comput Programs Biomed 1977;7:41–4.

10. Zar JH. Bicstatistical analysis. New Jersey: Prentice Hall, 1984.

11. Williams R. Drug administration in hepatic disease. N Engl J Med 1984;309:1616–22.

12. Haberer JP, Schoeffler P, Couderc E, Duvaldestin P. Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. Br J Anaesth 1982;54:1267.

13. Patwardhan RV, Johnson RF, Hoyumpa A Jr, et al. Normal metabolism of morphine in cirrhosis. Gastroenterology 1981;81:1006–11.

14. Shelly MP, Cory EP, Park GR. Pharmacokinetics of morphine in two children before and after liver transplantation. Br J Anaesth 1986;58:1218–23.

15. Williams RL, Benet LZ. Drug pharmacokinetics in cardiac and hepatic disease. Annu Rev Pharmacol Toxicol 1980;20:389–413.

16. Marshall JS, Williams S. Serum inhibitors of desialylated glycoprotein binding to hepatocyte membranes. Biochim Biophys Acta 1978;543:41–52.

17. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 1982;54:871–7.

18. Bovill JG, Sevel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R 39209): A new opioid analgesic. Anesthesiology 1982;57:439–43.

19. Chauvin M, Sandouk P, Scherrmann JM, Farinotti R, Strumza P, Duvaldestin P. Morphine pharmacokinetics in renal failure. Anesthesiology 1987;66:327–31.

20. Chauvin M, Lebrault C, Levron JC, Duvaldestin P. Pharmacokinetics of alfentanil in chronic renal failure. Anesth Analg 1987;66:53–6.

21. Davis PJ, Stiller RL, Cook DR, Brandom BW, Davin-Robinson KA. Pharmacokinetics of sufentanil in adolescent patients with chronic renal failure. Anesth Analg 1988;67:268–71.

Sufentanil Does Not Block Sympathetic Responses to Surgical Stimuli in Patients Having Coronary Artery Revascularization Surgery

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SONNTAG H, STEPHAN H, LANGE H, RIEKE H, KETTLER D, MARTSCHAUSKY N. Sufentanil does not block sympathetic responses to surgical stimuli in patients having coronary artery revascularization surgery. Anesth Analg 1989;68:584–92.

The effects of a moderate dose of sufentanil (1 $\mu g \cdot kg^{-1}$ + 0.015 $\mu g \cdot kg^{-1} \cdot min^{-1}$) plus nitrous oxide (30% O_2/ 70% N_2O) anesthesia (group I; n = 8) and of high-dose sufentanil/O_2 anesthesia (10 $\mu g \cdot kg^{-1}$ + 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) without N_2O (group II; n = 8) on cardiovascular dynamics, myocardial blood flow, myocardial oxygen consumption, myocardial lactate balance, and hypoxanthine release were studied in two groups of male patients scheduled for elective coronary artery bypass surgery. All patients were on maintenance doses of calcium channel blockers and nitrates with the last doses of medications given the morning of operation. All patients were premedicated with flunitrazepam (2 mg orally), piritramide (7.5 mg IM) and promethazine (25 mg IM). Measurements were performed before the induction of anesthesia with the patients premedicated but awake; 20 min after induction of anesthesia with sufentanil plus pancuronium 0.1 $mg \cdot kg^{-1}$ for muscle relaxation before surgery; and during sternotomy and sternal spread. Sufentanil at either dose decreased mean arterial pressure, as well as cardiac and stroke volume index while heart rate remained unchanged. Following the induction myocardial blood flow and myocardial oxygen consumption decreased 23% (79 $ml \cdot min^{-1} \cdot 100 \ g^{-1}$ to 61 $ml \cdot min^{-1} \cdot 100 \ g^{-1}$ and 28% (9.2 ml $O_2 \cdot min^{-1} \cdot 100 \ g^{-1}$ to 6.6 ml $O_2 \cdot min^{-1} \cdot 100 \ g^{-1}$) in group I and 14% (78 $ml \cdot min^{-1} \cdot 100 \ g^{-1}$ to 67 $ml \cdot min^{-1} \cdot 100 \ g^{-1}$ and 18% (8.7 ml $O_2 \cdot min^{-1} \cdot 100 \ g^{-1}$ to 7.1 ml $O_2 \cdot min^{-1} \cdot 100 \ g^{-1}$) in group II. Myocardial ischemia was seen in one patient of group II (patient No. 4), as indicated by a hypoxanthine release into the coronary sinus, when after the induction MAP decreased from 93 to 67 mm Hg and heart rate increased from 56 to 71 min^{-1}. During sternotomy 8 of 16 patients (50%) developed hypertension and 9 of 16 patients (56%) showed signs of myocardial ischemia, i.e., a lactate and/or hypoxanthine release. Ischemia was related to hypertension in three patients but occurred in six patients without significant alterations in heart rate, PAP, PCWP, or arterial pressures. These data demonstrate that sufentanil, like fentanyl, produces incomplete anesthesia in patients with coronary heart disease and is not able to protect the myocardium adequately from autonomic sympathetic responses, even though sufentanil has the advantage of having more rapid onset of action than fentanyl.

Key Words: ANESTHESIA—cardiac.
ANESTHETICS, INTRAVENOUS—sufentanil.
HEART—blood flow, oxygen consumption.
SURGERY—coronary artery bypass grafting.

Sufentanil is a synthetic opioid of particular interest as an anesthetic for patients with coronary artery or valvular heart disease because of its specificity as an analgesic and its lack of cardiovascular side effects (1–3). These characteristics derive from a significantly higher affinity to stereospecific binding sites with minimal degree of non-specific binding activities and a slower dissociation from the receptor than fentanyl (4). The higher analgetic potency (5) and receptor specificity of sufentanil have been suggested as providing better blockade of uncontrolled cardiovascular responses to noxious stimuli than fentanyl, which, even in high doses, may not prevent hypertension

Table 1. Patient Data

Group	Sex	Age	Body surface area (m²)	ASA physical status	Cardiac Meds	Previous Infarction	EF (%)	LVEDP (mm Hg)	Grafts
1	M	54	1.97	III	Ni/N	1	55	13	4
1	M	56	2.01	III	D/N	1	50	12	3
1	M	38	1.71	II	D/N	1	65	13	2
1	M	51	1.93	II	Ni/N	0	70	12	3
1	M	56	1.92	III	Ni/N	2	55	14	3
1	M	47	1.97	III	Ni/N	2	55	13	2
1	M	47	2.05	II	D/N	0	65	12	3
1	M	56	2.03	III	Ni/N	1	55	13	4
2	M	46	1.92	III	Ni/N	2	50	13	3
2	M	42	1.87	II	D/N	0	55	13	4
2	M	49	1.87	III	Ni/D	0	60	13	3
2	M	52	2.08	III	D/N	1	55	14	2
2	M	57	1.61	II	Ni/N	1	70	12	2
2	M	49	1.83	III	Ni/N	1	70	13	3
2	M	40	2.07	III	Ni/N	0	75	12	2
2	M	45	2.17	III	D/N	1	55	14	3

Abbreviations: Ni, nifedipine; D, diltiazem; N, nitrates; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure.

and tachycardia with associated changes in myocardial energy demand from occurring in response to surgical stimulation (6,7).

Slogoff and Keats (8) using analysis of the S-T segment during various types of anesthesia reported that myocardial ischemia could occur without any hemodynamic changes and that, while there was also a close relationship between myocardial ischemia and tachycardia, myocardial ischemia was not related to hypertension or hypotension. Their results emphasize the importance of the detection of ischemia in patients with coronary heart disease to optimize perioperative management. Other studies have revealed, however, that ECG changes are not always reliable for the detection of ischemia (9-11).

Because none of the previous studies has clearly established the relationship between hemodynamic stability and the dose of sufentanil required during coronary revascularization surgery, when used as a sole anesthetic in patients with coronary heart disease (12,13), this study was designed to investigate the effects of either a moderate dose of sufentanil combined with nitrous oxide or a high dose of sufentanil alone on myocardial blood flow, myocardial oxygen consumption and oxygen balance in patients undergoing coronary artery bypass surgery. In addition coronary blood flow, myocardial oxygen consumption and oxygen balance, lactate, and hypoxanthine (a degradation product of ATP and thus another sensitive marker of ischemia) were measured in the arterial and coronary venous blood as indices of anaerobic myocardial metabolism (14-16). Evaluation of the ECG as a less sensitive parameter was omitted from this study.

Methods

The study was approved by the Göttingen Human Subject Review Committee. Written informed consent was obtained from each patient at the time of the preoperative visit. In a randomized study one of two different doses of sufentanil (1 $\mu g \cdot kg^{-1}$ followed by 0.015 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 10 $\mu g \cdot kg^{-1}$ followed by 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered to one of two groups of patients with stable angina (ASA physical status II–III) scheduled for coronary artery bypass surgery. Each group consisted of eight males, ranging in weight from 52–91 kg (mean 76 kg) and from 66–90 kg (mean 79 kg) (Table 1). The moderate dose of sufentanil was administered to group I, the high dose to group II. There were no significant differences in age, weight, body surface area, and ASA physical status in the two groups. Four patients in group I and five patients in group II had angiographic evidence of left ventricular hypokinesis. No patient had a history of congestive heart failure, valvular heart disease, liver disease, or metabolic disorders. All patients were being treated with maintenance doses of calcium channel blockers (nifidepin 20–60 mg/d or diltiazem 120–180 mg/d) and nitrates (40–160 mg/d), the last doses of which were administered the morning of surgery.

All patients were premedicated with flunitrazepam (2 mg orally), piritramide (7.5 mg IM), and promethazine (25 mg IM) one hour before they arrived in the induction room. ECG leads (lead II) were attached and processed EEG (temporalparietal leads) was recorded in 30-second epochs (Schwarzer/Picker^ETM 2002/1264). Using the Seldinger technique under local anesthesia,

Table 2. Hemodynamic Variables and Blood Gas Tensions during Sufentanil Anesthesia (mean values and SEM)

	GROUP I					GROUP II				
	I	Int. + 1 min	Int. + 5 min	II	III	I	Int. + 1 min	Int. + 5 min	II	III
HR (L·min⁻¹)	63	65	65	61	63	63	64	63	64	60
	2	3	2	3	3	3	4	3	2	3
P_{syst} (mm Hg)	149	131	130	114*	155*†	138	127	124	110*	153*†
	2	6	4	6	6	5	6	5	5	6
MAP (mm Hg)	97	92	92	82*	106*†	93	89	86	82*	109*†
	2	2	3	4	5	3	3	2	5	5
MDAP (mm Hg)	86	79	78	74*	97*†	81	77	77	73*	98*†
	2	3	3	3	4	2	2	4	4	5
MPAP (mm Hg)	16.1	16.4	15.3	13.4	17.1†	16.9	16.8	15.8	14.6	18.8†
	1.9	1.4	1.5	1.4	2.3	1.6	1.7	1.9	1.9	1.2
PCWP (mm Hg)	8.6	8.7	8.3	8.5	10.9†	9.4	9.6	8.8	8.3*	11.1†
	0.3	0.3	0.8	0.6	0.7	0.4	0.9	0.9	0.4	0.6
CVP (mm Hg)	7.8	8.0	7.9	7.6	8.1	8.2	8.3	7.8	7.4	7.7
	0.4	0.5	0.5	0.4	0.6	0.5	0.4	0.5	0.6	0.6
CI (L·min⁻¹·m⁻²)	3.10	—	—	2.23*	2.31*	3.11	—	—	2.45*	2.33*
	0.09	—	—	0.11	0.09	0.15	—	—	0.16	0.11
SVI (mL·m⁻²)	49	—	—	37*	37*	49	—	—	38*	38*
	2	—	—	1	1	2	—	—	1	2
SVR [mm Hg/(mL·min⁻¹·kg⁻¹)]	1.28	—	—	1.40*	1.86*	1.16	—	—	1.26*	1.72*†
	0.05	—	—	0.08	0.16	0.05	—	—	0.05	0.19
Hb (g/dL)	13.6	—	—	12.9*	12.7*	13.7	—	—	13.1*	13.1*
	0.3	—	—	0.3	0.3	0.4	—	—	0.4	0.4
Ht (%)	41.1	—	—	38.5*	37.6*	41.5	—	—	39.7*	38.5*†
	1.6	—	—	0.9	1.0	1.6	—	—	1.3	1.4
pO₂cor.ven. (mm Hg)	23.5	—	—	25.2	25.1	23.8	—	—	23.2	24.6
	0.5	—	—	0.4	1.0	0.8	—	—	0.5	0.9
p_aO_2 (mm Hg)	92.6	—	—	107.9*	121.0*†	89.5	—	—	110.1*	122.5*†
	9.9	—	—	3.1	8.7	3.7	—	—	4.9	7.3
p_aCO_2 (mm Hg)	41.6	—	—	40.9	40.9	42.5	—	—	39.2	39.6
	0.7	—	—	0.8	0.5	0.7	—	—	0.6	0.6
pH_a	7.35	—	—	7.37	7.37	7.34	—	—	7.39	7.39

*$P < 0.05$, awake vs II and awake vs III; †$P < 0.05$, II vs III.

HR, heart rate; P_{syst}, systolic pressure; MAP, mean arterial pressure; MDAP, mean diastolic arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; Hb, hemoglobin; Ht, hematocrit; pH, H^+ activity (44.6 ± 1.2; 42.8 ± 1.4; 42.9 ± 1.6 in group I and 44.1 ± 1.0; 43.2 ± 1.2; 43.3 ± 1.2 in group II, respectively); I, awake values; II, after induction of anesthesia; III, sternotomy.

a Goodale-Lubin (USCI-6F) catheter was inserted via the right internal jugular vein into the coronary sinus for measurement of myocardial blood flow and for withdrawal of blood samples; an 18-gauge catheter, connected to a Goodale-Lubin catheter (USCI-6F), was inserted into the radial artery of the non-dominant side; a Swan-Ganz catheter (Edwards quadruple thermodilution model No. 93 A 131-7F) was inserted via a left antecubital vein into the pulmonary artery; and a polyurethane catheter was placed in the superior vena cava for fluid and drug infusion. The positions of all catheters was confirmed by fluoroscopy. ECG, body temperature, and all pressures were monitored continuously and recorded simultaneously on a 10-channel strip chart recorder (Hellige, Freiburg).

After infusion of 500 ml saline anesthesia was induced with sufentanil 1 $\mu g\cdot kg^{-1}$ as a bolus dose within 2 minutes, followed by an infusion of 0.015

$\mu g\cdot kg^{-1}\cdot min^{-1}$ in group I and with 10 $\mu g\cdot kg^{-1}$ as bolus dose and 0.15 $\mu g\cdot kg^{-1}\cdot min^{-1}$ as infusion in group II. No additional hypnotics were used. Patients were breathing 100% oxygen with respirations assisted using a face mask to maintain p_aCO_2 at 38 to 40 mm Hg (5–5.3 kPa) as confirmed by arterial blood gas analysis. After patients lost consciousness, tracheal intubation was facilitated by 0.1 $mg\cdot kg^{-1}$ pancuronium and controlled ventilation with O_2/N_2O (30%/70%) in group I and with 30% oxygen in air in group II was instituted using a volume-constant respirator (Engström ER 300). Patients in group I received a total dose of 1.8 $\mu g\cdot kg^{-1}$ of sufentanil, while patients in group II received a total dose of 17.5 $\mu g\cdot kg^{-1}$ of sufentanil until sternotomy.

After a 15-minute period of rest measurements were performed and blood samples obtained: 1) with the patients awake (measurement I); 2) 20 minutes after the induction of anesthesia (measurement II);
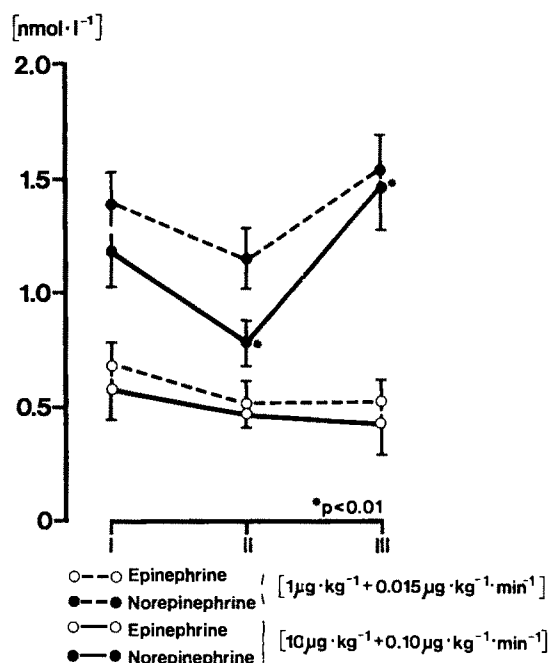
Figure 1. Plasma epinephrine and norepinephrine levels in the awake patient (measurement I), after induction of anesthesia (measurement II), and during sternotomy and sternal spread (measurement III); mean values and SEM.

and 3) during sternotomy and sternal spread (measurement III). An average of 45 ± 5 min elapsed between measurements I and III.

Measurements in this study included myocardial blood flow (MBF) measured in duplicate using the argon wash-in technique (coefficient of variation ±5.1%) with continuous and simultaneous sampling (via a modified syringe pump Unita I, Braun Comp.) from the radial artery and the coronary sinus after inhalation of a standard concentration of argon (17,18); cardiac output (mean value of five measurements during endexspiratory pauses) by thermodilution using the pulmonary artery catheter and a cardiac output computer (Fischer HZV Mod.BN 760); mean arterial pressure (MAP); mean pulmonary artery pressure (MPAP); pulmonary capillary wedge pressure (PCWP); right atrial pressure (RAP), and coronary sinus pressure (PCS) (Statham P23 IA).

Immediately before and after each measurement of coronary blood flow arterial and coronary venous blood samples were taken and analyzed for hemoglobin concentration, oxygen saturation and content (CO-oximeter IL 282 and Lex-O_2-Con, IL), blood gas tensions (standard electrodes, Radiometer), and plasma levels of epinephrine and norepinephrine (HPLC-EC, Bioanalytical systems; coefficient of variation ±9.4%), lactate (enzymatically; coefficient of variation ±2.9%), and Na^+, K^+, Mg^{++}, and Ca^{++} (atom absorption spectrophotometry, Perkin Elmer

303). Plasma levels of hypoxanthine, a degradation product of ATP formed under anaerobic conditions and as such a sensitive marker of ischemia (14,15), were measured using a modification of the method of Harmsen et al. (19): after deproteinization and buffering to pH 5–7, the aqueous supernatant was injected into the HPLC-system, consisting of a gradient pump (Merck-Hitachi 655-12 Chromatograph; L 5000 LC controller) and an autosampling and injection device (Merck-Hitachi 655 A-40 Autosampler). For separation a Merck LiChrospher 100 RP 18 5-μm column with a length of 250 mm was used. Detection wavelength was 248 nm (Merck-Hitachi 655, variable wavelength UV-detector). Data processing was performed using an automatic plotting and integration device (Merck-Hitachi D2000 Chromato-Integrator). Intraserial reproducibility was provided with 10 identical samples prepared separately. The intraserial coefficient of variation was ±2.1% at 2.7 $\mu M \cdot l^{-1}$.

Derived variables were calculated as follows: coronary vascular resistance (CVR) as mean diastolic arterial pressure (MDAP) minus coronary sinus pressure (PCS) divided by MBF. Myocardial oxygen consumption (MVO_2) was calculated by multiplying arterial-coronary venous oxygen content difference by MBF. Blood oxygen content was measured directly with the Lex-O_2-Con and was calculated from hemoglobin concentration, O_2-saturation, and O_2-tension to verify the obtained values. Lactate uptake and release were calculated by multiplication of the arterial-coronary venous blood lactate difference by MBF.

Statistical analysis of the obtained data in each group was performed using the Wilcoxon matched-pairs signed-ranks test; $P < 0.05$ was assigned statistical significance. The Mann-Whitney U-test was used for group comparisons. To adjust for multiple testing the Holm procedure (20) was used with overall significance $P < 0.05$.

Results

Hemodynamic and arterial blood gas data are presented in Table 2. Two patients in group I and three patients in group II developed hypertension with systolic peak pressures of more than 180 mm Hg requiring vasodilator therapy after sternotomy.

During laryngoscopy and tracheal intubation the hemodynamic data were not significantly different from preinduction values. Plasma levels of epinephrine and norepinephrine were lower after induction of anesthesia than in the awake state in both groups, but only the decrease of norepinephrine level in

Table 3. Myocardial Variables during Sufentanil-O_2-N_2O Anesthesia

Group I	MBF (mL·min⁻¹·100 g⁻¹)			MVO₂ (mL·min⁻¹·100 g⁻¹)			O₂Sat.cor.ven. (%)			CVR [mm Hg/ (mL·min⁻¹·100 g⁻¹)]			PCWP (mm Hg)			Lactate (μM·min⁻¹·100 g⁻¹)		
Patients	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	76	66	81	8.5	6.4	7.6	33.9	38.1	42.4	1.07	1.01	1.69	8.2	8.6	8.9	1.3	0.7	±0°
2	79	59	64	9.6	6.2	6.3	30.3	36.3	39.2	1.02	1.41	1.48	8.1	8.4	8.6	4.2	3.3	0.9
3	90	59	78	10.2	6.7	8.1	32.0	30.9	33.4	1.06	1.49	1.34	8.4	8.3	10.5	6.1	10.0	3.3°
4	68	61	94	7.8	6.9	9.4	34.3	42.4	37.9	1.27	1.01	1.05	8.3	8.2	11.2	7.8	1.8	5.9
5	74	57	64	8.6	6.5	6.2	35.8	39.2	33.4	1.06	1.04	1.26	8.5	9.6	12.6	6.1	2.0	−1.3°
6	72	61	104	8.1	6.5	11.4	35.4	37.5	36.0	1.12	0.99	0.97	8.5	8.3	10.1	12.4	1.2	6.2
7	86	54	92	10.1	5.7	9.1	30.2	35.0	39.6	0.95	1.10	0.93	10.9	8.0	11.0	3.1	3.8	7.4
8	88	60	86	10.5	7.7	12.7	28.1	32.5	24.2	0.98	0.95	1.19	8.0	10.5	14.3	8.8	6.6	−7.7°
Mean	79	61*	83†	9.2	6.6*	8.9†	32.5	36.5*	35.7*	1.07	1.13	1.24†	8.6	8.7	10.9†	6.2	3.7	1.8
SEM	3	1	5	0.4	0.2	0.8	1.0	1.3	2.0	0.03	0.07	0.09	0.3	0.3	0.7	1.2	1.1	1.7

*$P < 0.05$, awake vs II and awake vs III; †$P < 0.05$, II vs III; °Hypoxanthine release; MBF, myocardial blood flow; MVO₂, myocardial oxygen consumption; O₂Sat.cor.ven., coronary sinus oxygen saturation; CVR, coronary vascular resistance; PCWP, pulmonary capillary wedge pressure; Lactate, myocardial lactate uptake or release (−).
I, awake values; II, 1 μg·kg⁻¹ + 0.015 μg·kg⁻¹·min⁻¹ Sufentanil; III, sternotomy.

Table 4. Myocardial Variables during High-dose Sufentanil-O_2/Air Anesthesia

Group II	MBF (mL·min⁻¹·100 g⁻¹)			MVO₂ (mL·min⁻¹·100 g⁻¹)			O₂Sat.cor.ven. (%)			CVR [mm Hg/ (mL·min⁻¹·100 g⁻¹)]			PCWP (mm Hg)			Lactate (μM·min⁻¹·100 g⁻¹)		
Patients	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	87	72	94	8.6	7.7	9.2	31.8	31.9	37.3	1.07	1.01	1.96	8.2	8.7	11.3	7.9	12.6	1.1°
2	71	62	71	7.2	6.6	8.2	37.7	42.6	39.1	1.27	1.17	1.57	9.6	8.2	12.1	2.4	1.2	−1.1°
3	69	67	75	8.6	7.5	9.1	32.3	37.3	35.7	1.14	1.03	1.19	8.3	8.2	12.2	6.7	4.5	−7.3°
4	67	75	94	8.1	9.0	12.8	33.7	30.1	28.9	1.09	0.92	1.09	8.8	6.4	11.7	4.4	1.9°	−4.9°
5	89	63	104	9.4	6.6	10.8	30.1	30.4	31.2	0.75	0.79	1.43	9.5	9.6	12.9	8.0	3.8	4.4
6	81	64	99	10.4	7.3	9.9	37.4	40.7	39.4	0.95	0.92	0.82	8.6	7.4	7.6	3.2	1.9	3.5
7	73	55	88	8.5	5.8	10.3	31.5	36.4	33.6	0.94	1.01	0.93	10.3	8.4	9.7	4.8	1.1	3.1
8	83	77	128	8.7	6.3	11.6	36.2	40.6	35.4	1.12	1.22	1.31	11.6	9.5	12.6	6.3	4.0	±0°
Mean	78	67*	93*†	8.7	7.1*	10.2*†	33.8	36.3*	35.1*	1.04	1.01	1.29†	9.4	8.3*	11.2†	5.5	3.9	−0.16
SEM	3	3	6	0.3	0.4	0.5	1.0	1.5	1.3	0.06	0.05	0.10	0.4	0.4	0.6	0.7	1.3	1.3

*$P < 0.05$, awake vs II and awake vs III; †$P < 0.05$, II vs III; °Hypoxanthine release; MBF, myocardial blood flow; MVO₂, myocardial oxygen consumption; O₂Sat.cor.ven., coronary sinus oxygen saturation; CVR, coronary vascular resistance; PCWP, pulmonary capillary wedge pressure; Lactate, myocardial lactate uptake or release (−).
I, awake values; II, 10 μg·kg⁻¹ + 0.15 μg·kg⁻¹·min⁻¹ Sufentanil; III, sternotomy.

group II was statistically significant (Fig. 1). While epinephrine levels did not change throughout the study, norepinephrine levels were significantly elevated in group II during sternotomy.

In Tables 3 and 4 individual and mean values of the myocardial variables are presented. In Tables 5 and 6 arterial and coronary lactate and hypoxanthine concentrations are given. Following induction of anesthesia the arterial coronary venous oxygen content difference was significantly reduced in both groups together with a significant increase in coronary venous oxygen saturation. Although a negative lactate balance was not observed at that time, there was a release of hypoxanthine into the coronary sinus in patient No. 4 of group II, in whom the induction of anesthesia was followed by a decrease in mean arte-

rial pressure from 93 to 67 mm Hg and an increase in heart rate from 56 to 71 min⁻¹. At this time there were no statistical differences between the variables of groups I and II.

During sternotomy and sternal spread myocardial lactate production and hypoxanthine release were observed in two patients of group I (Nos. 5 and 8). In patient No. 1, in whom neither a lactate uptake nor a release were found, the coronary venous hypoxanthine level exceeded the arterial level, whereas in patient No. 3 of group I a hypoxanthine release was combined with a positive lactate balance.

Lactate production was also observed in three patients (Nos. 2, 3, and 4) of group II during sternotomy, which correlated with a hypoxanthine release at the same time, while in patient No. 8 hypoxanthine

Table 5. Lactate Concentrations (mM/l)

Group I patients	art.	cor.ven.	art.	cor.ven.	art.	cor.ven.
		I		II		III
1	1.61	1.43	1.62	1.52	1.66	1.66
2	1.64	1.11	1.66	1.10	1.61	1.47
3	1.64	0.96	1.75	1.58	1.71	1.29
4	1.58	0.43	1.62	1.34	1.78	1.15
5	1.67	0.85	1.76	1.40	1.68	1.88
6	1.75	0.03	1.66	1.46	1.64	1.04
7	1.70	1.34	1.77	1.06	1.81	1.01
8	1.67	0.67	1.65	0.55	1.75	2.64
Mean	1.66	0.85	1.69	1.25	1.71	1.52*
SEM	0.02	0.17	0.02	0.12	0.03	0.19
Group II		I		II		III
1	1.65	0.74	1.82	0.07	1.90	1.78
2	1.66	1.32	1.62	1.42	1.64	1.80
3	1.64	0.66	1.64	0.97	1.66	2.63
4	1.51	0.85	1.54	1.29	1.62	2.14
5	1.69	0.80	1.66	1.06	1.72	1.30
6	1.62	1.23	1.62	1.33	1.65	1.29
7	1.73	1.07	1.67	1.47	1.74	1.39
8	1.54	0.79	1.59	1.08	1.64	1.64
Mean	1.63	0.93	1.64	1.08	1.69*†	1.75*†
SEM	0.03	0.09	0.03	0.16	0.03	0.16

*0.05, awake vs II and awake vs III; †0.05, II vs III.

Table 6. Hypoxanthine Concentrations (mM/l)

Group I patients	art.	cor.ven.	art.	cor.ven.	art.	cor.ven.
		I		II		III
1	2.55	2.47	2.70	2.59	3.03	3.54
2	1.25	1.18	1.83	1.52	1.53	1.47
3	2.65	2.35	2.13	1.95	2.02	2.55
4	2.21	2.05	2.18	2.13	2.28	2.20
5	1.89	1.81	2.31	2.24	2.29	2.45
6	1.35	1.22	1.84	1.73	2.01	1.92
7	2.37	1.82	2.35	2.23	2.68	2.57
8	3.31	3.27	3.79	3.63	3.77	4.09
Mean	2.20	2.02	2.39	2.25	2.45	2.60*
SEM	0.24	0.25	0.22	0.23	0.25	0.30
Group II		I		II		III
1	3.09	2.84	3.34	3.16	3.35	4.17
2	2.53	1.96	2.78	1.86	2.93	3.82
3	2.56	2.48	2.70	2.63	2.74	3.04
4	2.10	1.91	1.26	1.88	2.24	3.23
5	3.35	2.63	2.34	2.07	2.12	1.47
6	1.81	1.21	1.59	1.28	2.02	1.27
7	2.76	2.12	2.86	2.57	3.21	2.95
8	2.32	2.19	2.49	1.62	1.96	2.34
Mean	2.66	2.17	2.42	2.13	2.57	2.79†
SEM	0.24	0.18	0.24	0.22	0.20	0.37

*$P < 0.05$, awake vs II and awake vs III; †$P < 0.05$, II vs III.

was released into the coronary sinus at an even lactate balance and in patient No. 1 at a declining but still positive lactate balance. However, again there were no statistical differences between groups I and II in measurements III. The correlation (Fig. 2) between lactate and/or hypoxanthine release and pulmonary capillary wedge pressure was only poor (r = 0.62). During the entire study period plasma electrolyte
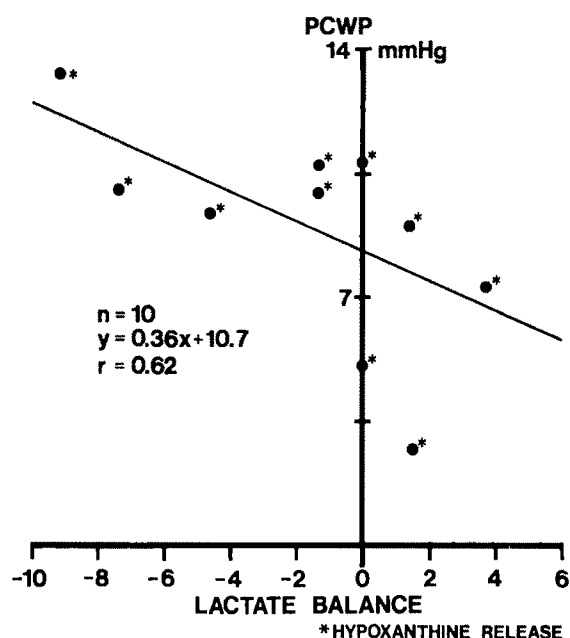
Figure 2. All patients with negative lactate balance demonstrated a release of hypoxanthine. However, there was only a poor correlation (r = 0.62) between the increase in pulmonary capillary wedge pressure and lactate and/or hypoxanthine release into the coronary sinus blood.

concentrations, blood gas tensions, pH, and body temperature stayed within normal ranges.

In the EEG both doses of sufentanil led to decreases in the number of higher-frequency waves and increases in lower-frequency (delta) waves, which did not change in the course of the study. No patient had signs of awareness and no patient remembered any aspect of the operation.

The average total dose of pancuronium given until sternotomy was 16 mg. The duration of operation averaged 264 ± 42 min. All patients required mechanical ventilation for 5-12 hours postoperatively. No patient in either group had signs of perioperative myocardial infarction.

Discussion

Our data demonstrate that a moderate dose of sufentanil (1 μg·kg^{-1} plus 0.015 μg·kg^{-1}·min^{-1}) combined with nitrous oxide as well as a high dose (10 μg·kg^{-1} plus 0.15 μg·kg^{-1}·min^{-1}) without nitrous oxide are associated with minimal but statistically significant changes in cardiovascular dynamics in patients with coronary artery disease undergoing coronary artery surgery. In spite of different demographic data of patients, different anesthetic techniques, different preoperative therapy, and premedication, these hemodynamic changes are comparable to the results of

other authors (12,13,21), but prior to this there was only one clinical study (3) of the effects of sufentanil on myocardial blood flow and myocardial energy balance in patients with coronary heart disease during the induction of anesthesia but not under surgical stress, which is of major importance and thus the main subject of our investigation.

Following the induction of anesthesia, mean arterial pressure decreased significantly in both groups, while changes of MPAP and PCWP were negligible. Heart rate remained unchanged during the entire study period, even during laryngoscopy and intubation. This may be because pancuronium counteracted the negative chronotropic effect of the opioids and/or because of the pharmacologic pretreatment of the patients with calcium channel blockers, which could have an influence on spontaneous sinus node activity and on atrioventricular conduction time (22). Laryngoscopy and tracheal intubation led to a transitory increase of blood pressure but not above the awake values. The fact that patients in group I tended to have a lower systolic and mean arterial pressure after induction is probably related to the cardiodepressant effect of nitrous oxide in combination with sufentanil (23,24). Wynne et al. (25) observed a slight reduction in dP/dt$_{max}$, cardiac output and heart rate during elective cardiac catheterization in patients with ischemic heart disease receiving 50% N_2O, which they attributed to a reduction of sympathetic activity by nitrous oxide.

There are striking differences between our results and those of Sebel et al. (2) and Bovil et al. (26) as to CI, SVI, and SVR. Neither in patients with coronary artery disease nor in patients with valvular heart disease did they find changes of these variables with sufentanil, 19.5 μg·kg^{-1}, except that systemic vascular resistance increased significantly during sternotomy (2). The reason for these differences is not clear but could be based on different anesthetic techniques and times at which measurements were made.

Our study demonstrates that both a moderate dose of sufentanil combined with nitrous oxide and a high dose of sufentanil without nitrous oxide, produce adequate anesthesia as shown by the typical EEG changes, but that neither block sympathetic responses to noxious stimuli in patients with coronary heart disease. Thus it does not fulfill anesthetic requirements for this kind of surgery and so sufentanil offers no advantage over fentanyl, which likewise produces cardiovascular instability during noxious stimulation (6,7). During sternotomy systemic vascular resistance, mean arterial pressure, and coronary perfusion pressure rose considerably in both our groups of patients, whereas heart rate, cardiac index, and stroke volume index did not change significantly

compared to the postinduction values. Our results do not support the finding of others, that sufentanil is superior to fentanyl with regard to hemodynamic stability even under surgical stimulation (1,26).

Both doses of sufentanil, however, reduced sympathoadrenal activity as is shown by the plasma catecholamine levels, which decreased after induction in both groups, but only the decrease of the norepinephrine level in group II was statistically significant. Sternotomy did not lead to an increase of epinephrine above the postinduction concentration, while the norepinephrine concentration at that time exceeded the awake value in group II. Because it is mainly released from peripheral sympathetic nerve endings from where there is rapid uptake, the plasma levels of norepinephrine do not reflect its concentration at the site of action in postsynaptic receptors. Therefore no close correlation could be found with the degree of hypertension. Our results differ from those of Sebel et al. (27) and confirm those of Howie et al. (12) and Murkin et al. (21). The latter observed no changes in norepinephrine and epinephrine levels during the prebypass period. Even in patients that became hypertensive during sternotomy no significant increases in plasma catecholamines could be demonstrated by them.

Hemodynamic alterations during sufentanil anesthesia in patients with coronary artery disease may lead to myocardial ischemia. Litak et al. (28) recorded ECG leads V_6 and V_9 continuously with a Holter monitor for the detection of myocardial ischemia in connection with changes of blood pressure and heart rate in patients anesthetized with 20 $\mu g \cdot kg^{-1}$ sufentanil. In 26% of their patients prebypass myocardial ischemia developed, along with bradycardia and hypertension and hypotension.

As a result of the diminished myocardial work load due to the hemodynamic changes in this study, the induction of anesthesia with sufentanil led to a 28% reduction of left ventricular oxygen consumption in group I and an 18% reduction in group II, the difference being the result of a higher pressure load on the left ventricle in group I leading to a higher oxygen consumption in the awake state than in patients of group II. Coronary blood flow decreased by 23% and 14%, respectively, while the coronary-venous oxygen saturation increased. These data, together with a positive lactate balance, indicate an adequate oxygen supply to the left ventricle during the postinduction period. However, since normoxic areas still may extract lactate from coronary blood, while ischemic areas may release lactate simultaneously into coronary sinus blood, which mixes with the blood from normoxic areas, global lactate balance

may remain positive despite regional myocardial ischemia (29). Thus only a negative lactate balance allows a definite conclusion about myocardial ischemia. Our results suggest that oxygen demand and supply were kept in equal balance in most patients after induction of anesthesia (measurement II). One exception was patient No. 4 of group II, in whom hypoxanthine was released into the coronary sinus in spite of a positive lactate balance, indicating regional myocardial ischemia, which may be explained by an increase in heart rate by 22% and a decrease in mean arterial pressure by 28%. The 12% increase in myocardial blood flow obviously was not able to compensate for this in the poststenotic parts of the coronary vessels, although the overall oxygen supply increased by 11% as indicated by a decrease in coronary venous oxygen saturation and an increase in arterial-coronary venous oxygen content difference.

Contrary to the small metabolic changes of the postinduction period, lactate and hypoxanthine releases were observed in two patients of group I (Nos. 5 and 8) and in three patients of group II (Nos. 2, 3, and 4) during sternotomy and sternal spread. In all of these patients myocardial ischemia was combined with increases of systolic peak pressures up to 180 mm Hg but stable heart rates. In two more patients (No. 3 of group I and No. 1 of group II), hypoxanthine release was seen in connection with a still positive but declining lactate balance, thus also indicating myocardial ischemia during this period. In patients No. 1 of group I and No. 8 of group II neither a lactate uptake nor release but rather a hypoxanthine release was observed. In these patients the development of myocardial ischemia was not related to hemodynamic changes, i.e. these patients developed neither hypertension or hypotension nor tachycardia or bradycardia by more than ±10% during sternotomy as compared to postinduction values. Thus, myocardial ischemia in these patients cannot be explained by changes in the hemodynamic determinants of myocardial oxygen consumption. Noxious stimuli such as sternal spread and manipulations at the aortic root may lead to a redistribution of coronary blood flow from the subendocardium to epicardial zones, resulting in regional ischemia. The significant increase in coronary vascular resistance with both doses of sufentanil, the individual morphology of the coronary artery stenosis as well as alpha-adrenergic mechanisms might have played a role in these patients (30–32). The clinical significance of this redistribution concept is supported by the results of the study, demonstrating an increase in coronary vascular resistance, elevated norepinephrine plasma

levels compared to the postinduction values and the occurrence of myocardial ischemia.

In conclusion, our findings demonstrate that sufentanil, either at a moderate dose combined with nitrous oxide or at a high dose as a sole anesthetic, is not able to prevent hypertension associated with sternotomy. During sternotomy 42% of the patients developed hypertension and 56% showed signs of myocardial ischemia, i.e., a lactate and/or hypoxanthine release into the coronary sinus. In this respect, sufentanil is no different from fentanyl in patients with coronary heart disease (5). Sufentanil acts more rapidly than fentanyl (1) and produces unconsciousness in all patients, but despite this anesthesia with sufentanil alone, without supplementation by a suitable sedative agent for total intravenous anesthesia or by inhalational anesthetics for balanced anesthesia, it cannot be recommended for patients undergoing coronary artery bypass surgery.

References

1. De Lange S, Boscoe MJ, Stanley ThH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology 1982;56:112–8.

2. Sebel PS, Bovil JG. Cardiovascular effects of sufentanil anesthesia. Anesth Analg 1982;61:115–9.

3. Miller DR, Wellwood M, Teasdale SJ, Laidley D, Ivanov J, Young P, Madonik M, McLaughlin P, Mickle DAG, Weisel RD. Effects of anaesthetic induction on myocardial function and metabolism: a comparison of fentanyl, sufentanil and alfentanil. Can J Anaesth 1988;35:219–33.

4. Leysen JE, Gammeren W, Niemegeers CJE. [^{3}H] Sufentanil, a superior ligand for μ-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. Eur J Pharmacol 1983;87:209–25.

5. Niemegeers CJE, Schellekens KHL, von Bevern WFM, Janssen PAJ. Sufentanil, a very potent and extremely safe intravenous morphin-like compound in mice, rats and dogs. Arzneim.-Forsch. (Drug Res) 1982;26:112–8.

6. Sonntag H, Larsen R, Hilfiker O, Kettler D, Brockschnieder B. Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients with coronary artery disease. Anesthesiology 1982;56:417–22.

7. Waller JL, Hug CC, Nagle DM, Craver JM. Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operation. Anesthesiology 1981;55:212–7.

8. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.

9. Bellows WH, Bode RH jr, Levy JH, Foex P, Philbin D, Lowenstein E. Noninvasive detection of periinduction ischemic ventricular dysfunction by cardiokymography in humans: preliminary experience. Anesthesiology 1984;60:155–8.

10. Stern S, Tzivoni D, Stern Z. Diagnostic accuracy of ambulatory ECG monitoring in ischemic heart disease. Circulation 1975;52:1045–9.

11. Waters D, Forester JS. Myocardial ischemia, detection and quantification. Ann Intern Med 1978;88:239–50.

12. Howie MB, McSweeney TD, Lingam RP, Maschkes SP. A comparison of fentanyl-O_2 and sufentanil-O_2 for cardiac anesthesia. Anesth Analg 1975;65:877–87.

13. Rosow CE, Philbin DM, Keegan CR, Moss MAJ. Hemodynamics and histamine release during induction with sufentanil or fentanyl. Anesthesiology 1984;60:489–91.

14. De Jong JW. Biochemistry of acutely ischemic myocardium. In: Scharper W, ed. The Pathophysiology of Myocardial Perfusion. New York: Elsevier/North Holland, 1979:719–50.

15. Fox AC, Reed GE, Glassman E, Kaltman AJ, Silk BB. Release of adenosine from human hearts during angina produced by rapid atrial pacing. J Clin Invest 1974;53:1447–57.

16. Kugler G. Myocardial release of lactate, inosine and hypoxanthine during atrial pacing and exercise-induced angina. Circulation 1979;59:43–9.

17. Rau G. Messung der Koronardurchblutung mit der Argon-Fremd gasmethode. Arch Kreisl Forsch 1969;58:322–98.

18. Tauchert M, Kochsiek K, Heiss HW. In: Turin MA, ed. Measurement of coronary blood flow in man by the argon method; Myocardial blood flow in man. Minerva Medica 1970:859–64.

19. Harmsen E, de Jong JW, Serruys PW. Hypoxanthine production by ischemic heart demonstrated by high pressure liquid chromatography of blood purine nucleosides and oxypurines. Clin Chim Acta 1981;115:73–84.

20. Holm S. A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics 1979;6:65–70.

21. Murkin JM, Moldenhauer CC, Griesemer RW, Hug CC. Fentanyl vs sufentanil and catecholamine response during coronary artery surgery. Anesthesiology 1984;61:A375.

22. Kawai L, Konishi T, Matsuyama E, Okazaki H. Comparative effects of three calcium antagonists, diltiazem, verapamil and nifidepine, on sinoatrial and atrioventricular nodes. Circulation 1981;63:1035–42.

23. Lappas DG, Buckley MJ, Laver MB, Daggart WM, Lowenstein E. Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary artery surgery. Anesthesiology 1975;43:61–9.

24. Stoelting RK, Gibbs PS. Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary-artery disease. Anesthesiology 1973;38:45–52.

25. Wynne J, Mann T, Alpert JS, Green LH, Grossman W. Hemodynamic effects of nitrous oxide administered during cardiac catheterization. JAMA 1980;243:1440–3.

26. Bovil JG, Warren PJ, Schuller JL, van Wesel HB, Hoeneveld MH. Comparison of fentanyl, sufentanil, and alfentanil anesthesia in patients undergoing valvular heart surgery. Anesth Analg 1984;63:1081–6.

27. Sebel PS, Bovil JG, Fiolet JWT, Touben JL, Philbin DM. Hormonal effects of sufentanil on endocrine and metabolic responses to cardiac surgery. Anaesth Analg 1982;61:A215.

28. Litak CW, Fiona ER, Wynands JE, Ansley DM, Sami MH. Hemodynamic variables and the incidence of prebypass ischemia during sufentanil/O_2/pancuronium anesthesia in patients undergoing coronary artery surgery. J Cardiothoracic Anesth 1987;1:10–8.

29. Apstein CS, Gravino F, Hood WB. Limitation of lactate production as an index of myocardial ischemia. Circulation 1979;60:877–88.

30. Holtz J, Saeed M, Sommer O, Bassenge E. Norepinephrine constricts the canine coronary bed via postsynaptic α_2-adrenoreceptors. Eur J Pharmacol 1982;82:199–202.

31. Heusch G, Deussen A. The effects of cardiac sympathetic nerve stimulation on perfusion of stenotic coronary arteries in the dog. Circ Res 1983;53:8–15.

32. Heusch G, Deussen A, Thämer V. Cardiac sympathetic nerve activity and progressive vasoconstriction distal to coronary stenosis: feed back aggravation of myocardial ischemia. J Auton Nerve Syst 1985;13:311–26.

The Effect of pH and PCO$_2$ on Epidural Analgesia with 2% 2-Chloroprocaine

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ACKERMAN WE, JUNEJA MM, DENSON DD, KACZOROWSKI DM, SARRACINO S, LEE JI, NICHOLSON CJ, SCHIPPER J. The effect of pH and PCO$_2$ on epidural analgesia with 2% 2-chloroprocaine. Anesth Analg 1989;68:593-8.

Increasing the pH of local anesthetics with sodium bicarbonate has been reported to hasten their onset of action. The purpose of this study was to compare the onset and duration of epidural analgesia with the use of sodium bicarbonate and tromethamine to increase the pH of 2% chloroprocaine (2CP). Five groups of patients were studied: Group I received 2CP; Group II received 2CP buffered to a pH of 7.1 with tromethamine; Group III received 2CP buffered to a pH of 7.1 with sodium bicarbonate; Group IV received 2CP buffered to a pH of 7.7 with tromethamine; and Group V received 2CP buffered to a pH of 7.7 with sodium bicarbonate. The final pH and PCO$_2$ of each solution were measured.

Time to onset of analgesia was significantly delayed with either of the tromethamine buffered groups (II [5.6 ± 1.0 minutes] and IV [5.4 ± 0.4 minutes]) when compared with data from the unbuffered control (I [4.4 ± 0.1 minutes]) and the sodium bicarbonate buffered (III [4.5 ± 0.8 minutes] groups and Group V [2.7 ± 0.9 minutes]). Only when sodium bicarbonate buffer adjusted to pH 7.7 (Group

IV) was onset significantly more rapid than the unbuffered 2CP (I) and tromethamine buffered 2CP (II and IV). Multiple regression analysis revealed that onset times were significantly related to both pH and PCO$_2$. The coefficient of determination for this model was 0.5156. While duration of analgesia was significantly longer in the two tromethamine groups (II [59.1 ± 10.4 minutes] and IV [55.7 ± 4.5 min]) than in control (I [27.0 ± 6.1] and bicarbonate groups (III [29.5 ± 6.6 min] and V [26.2 ± 4.2 min]), there were no significant intergroup differences in the onset or duration of analgesia between the tromethamine buffered groups. Multiple regression analysis showed that duration was related to both pH and PCO$_2$. The coefficient of determination for this model was 0.7669.

Reasons for alterations in onset times appear to be complex, involving the use of 2CP solutions containing critical levels of PCO$_2$ and pH in addition to other currently unidentified albeit important factors. Prolongation of epidural analgesia appears to be heavily influenced by changes in pH, which by choice of alkalinizing agent can be fairly long lived.

Key Words: ANESTHETICS, LOCAL— 2-chloroprocaine. ANESTHETIC TECHNIQUES— epidural. PHARMACODYNAMICS, LOCAL ANESTHETICS—pH.

Conflicting reports of increasing the pH of local anesthetics with sodium bicarbonate for regional anesthesia has led to a serious clinical dichotomy (1–5). For example, increases in speed of onset and spread of sensory blockade have been reported for lidocaine solutions made alkaline with sodium bicarbonate (1).

Similar results have been reported with alkaline solutions of bupivacaine containing sodium bicarbonate (2). Alkaline bupivacaine solutions containing sodium bicarbonate have also been reported to prolong the duration of axillary block (3). Results with alkaline solutions of 2-chloroprocaine (2CP) containing sodium bicarbonate have been somewhat less convincing. One brief report claims a shorter onset time for epidural anesthesia with bicarbonate containing solutions, whereas a more detailed report showed no significant differences between the pH adjusted and control solutions (4,5). Although no PCO$_2$ values were reported for studies using lidocaine or bupiva-

caine, a PCO_2 of approximately 120 torr was reported with pH adjusted solutions of 2CP (5).

Because it is known that both pH and PCO_2 can alter the action of local anesthetics, we postulate that the combination of elevated PCO_2 and pH may be a critical factor in understanding the roles of pH and PCO_2 alone (6).

In an effort to determine the relative contributions of pH and PCO_2, we conducted a randomized, double-blind study to compare the onset and duration of epidural analgesia using sodium bicarbonate and tromethamine (tris[hydroxymethyl]aminomethane, THAM) buffered 2% 2-chloroprocaine solutions in patients requiring analgesia for the pain of labor.

Methods

Institutional Review Board approval and informed consent were obtained from 50 healthy ASA physical status I or II parturients who had requested epidural analgesia for labor. All epidural catheters were inserted at either the L2-3 or L3-4 interspaces and were advanced approximately 2-3 cm into the epidural space. Placements of catheters were performed with the use of a loss of resistance technique with air with patients in the sitting position. Prior to epidural placement, all patients were hydrated with 10 mL/kg of body weight of intravenous lactated Ringer's solution.

The patients were randomly assigned to one of five groups of 10 patients each prior to epidural placement: Group I: 2% 2CP, pH 4.35 with saline solution (3.0 mL/30 mL); Group II: 2CP buffered to pH of 7.1 with tromethamine (0.3M) (0.75 mL and 2.25 mL saline solution/30 mL); Group III: 2CP buffered to pH of 7.1 with sodium bicarbonate (8.4%) (1.0 mL and 2.0 mL saline solution/30 mL); Group IV: 2CP buffered to pH of 7.7 with tromethamine (0.3M) (1.7 mL and 1.3 mL saline solution/30 mL); Group V: 2CP buffered to pH of 7.7 with sodium bicarbonate (8.4%) (2.5 mL and 0.5 mL saline solution/30 mL). All of the 2CP solutions were bisulfite free. None of the solutions contained epinephrine. There was no precipitation of 2CP with the addition of the buffer solutions. Stability studies were conducted on all formulations by assaying solutions after preparation and 24 hours later. 2CP concentrations were measured with the use of gas chromatography as previously reported (7). Triplicate analyses were performed on each formulation. The present study consisted of evaluating only the first epidural dose. When patients complained of pain, they were judged to have completed the study and were given supplemental analgesia at the discretion of the responsible anesthesiologist.

Three milliliters of study solution were administered to each patient through the epidural catheter as a test dose followed. After 2 minutes, if the patient had no signs of an intravascular or subarachnoid injection and if attempts to aspirate blood or cerebrospinal fluid were negative, 5 mL of study solution were injected for a total volume of 8 mL. This volume was chosen to standardize the total dose and is the volume used to attain a T10-11 level when using the L2-3 or L3-4 interspaces with 2% 2CP at our institution. The posterior S2-3 dermatomes were tested bilaterally for analgesia to pinprick at time 0 and every 30 seconds thereafter until each patient reported loss of pain sensation to pinprick bilaterally. Time to onset of analgesia was defined as the time between administration of the initial test dose and the appearance of bilateral loss of pain sensation to pinprick in the S2-3 dermatomes. The duration of analgesia was defined as the time between onset of analgesia and pain with a uterine contraction. All patients were in active labor with contractions at least 2-3 minutes apart and with a verbal visual analog pain score (VAS) of >7 prior to epidural placement. A pre-block verbal response pain score (0-10; 0 = no pain and 10 = severe excruciating pain) was measured prior to placement of the epidural needle because it has been reported that the more intense the labor pain, the more rapid is the onset of epidural analgesia (8). The cephalad spread of the epidural blockade was measured bilaterally by pinprick after each patient reported analgesia at the S2-3 dermatomes. The pH and PCO_2 of the study solutions were measured with an ABL-30 blood gas analyzer (Radiometer, Copenhagen), whereas the specific gravity of the solutions was measured with a refractomometer. Monitoring of each patient consisted of a blood pressure and pulse measurements before epidural injection of 2CP and every 5 minutes for 15 minutes thereafter. Hypotension was defined as systolic blood pressure less than 80% of baseline levels or a systolic pressure less than 100 mm Hg. Motor scores before and after injection of 2CP were assessed with use of the Bromage scale (0 = full flexion of the knees and feet; 1 = able to move knees only; 2 = able to move the feet only; 3 = unable to move the feet or knees) (9).

All study solutions were administered in a double-blinded fashion.

Statistical Analysis

Interval data were analyzed for normalcy of distribution with the use of a Shapiro-Wilk W statistic.

Table 1. Intergroup Comparisons of Demographics and Preblock Characteristics

	Group I	Group II	Group III	Group IV	Group V
Age (yrs)[a]	21.5	21.3	22.2	22.3	23.9
	±4.9	±2.83	±4.59	±3.94	±4.09
Height (cm)[a]	164.58	162.29	161.55	161.50	164.41
	±9.41	±6.03	±10.51	±5.58	±6.5
Weight (kg)[a]	78.59	78.61	73.58	74.73	72.66
	±13.71	±12.82	±12.54	±5.26	±12
Gravidy[b]	1.5	2.0	2.0	2.0	2.0
	±0.6	±1.0	±1.0	±0.6	±1.0
Parity[b]	0.5	1.0	0.5	1.0	1.0
	±0.6	±0.6	−0.5	±0.5	±0.5
VAS pain score[b]	10.0	10.0	10.0	10.0	10.0
	±0.1	±0.5	±0.5	±0.5	±0.1
Cervical Dilation (cm)[b]	5.0	5.0	5.0	5.0	5.0
	±0.6	±0.5	±0.5	±0.6	±0.6

[a]Mean ± SD; [b]Median ± Quantile.

Depending on the results of this analysis, intergroup responses were compared with the use of either a parametric or non-parametric one-way analysis of variance followed by the appropriate critical value test for multiple comparisons. Ordinal data were analyzed with the use of a non-parametric one-way analysis of variance followed by the appropriate critical value test for multiple comparisons. Critical value tests were accomplished at significance levels of 0.05, 0.01, and 0.001. Stepwise multiple regression analysis was used to evaluate the effects of PCO_2, pH, and percent nonionized drug on the onset and duration of epidural analgesia with 2CP. Coefficients of determination (r^2) were used to evaluate the amount of variance explained by the model. Interval data are presented as means ± SD; ordinal responses as medians ± quantiles. A P value of 0.05 was considered the minimum level of statistical significance.

Results

All of the differences described next, which were found to be statistically significant, achieved a P value of <0.001.

The study groups did not differ significantly with respect to age, height, weight, gravity, parity, VAS pain scores, or cervical dilation (at the time of epidural placement) (Table 1). Intergroup differences in pH and PCO_2 values of the study solutions are summarized in Table 2. The specific gravities of the 2CP solutions were not significantly different (Table 2). There were no decreases in 2CP concentration in any of the five study solutions for at least 24 hours

after mixing. There were, however, significant losses in CO_2 from the groups buffered with bicarbonate after 24 hours. This loss of CO_2 was accompanied by a corresponding increase in pH. There were no intergroup differences with respect to motor scores in the levels of sensory analgesia (Table 2). One patient in the tromethamine buffered group (Group II) developed hypotension, which responded to a fluid bolus of 250 ml (Table 2).

The onset of analgesia was significantly longer in either of the tromethamine buffered groups (II [5.6 ± 1.0 minutes]; IV [5.4 ± 0.4 minutes]) than in the unbuffered control (I [4.4 ± 0.1 min]) and the sodium bicarbonate buffered (III [4.5 ± 0.8 minutes] and V [2.7 ± 0.9 minutes]) groups. Only in the sodium bicarbonate buffered group adjusted to pH 7.7 (V) was onset faster than in the unbuffered 2CP (I) and tromethamine buffered 2CP groups (II and IV). The bicarbonate groups differed significantly with reference to onset of analgesia (Fig. 1). Multiple regression analysis revealed that onset times were significantly related to both pH and PCO_2. The coefficient of determination for this model was 0.5156. Onset times predicted with the use of this model deviated randomly from those actually measured (Fig. 2).

Although the duration of analgesia was significantly longer with the two tromethamine groups (II [59.1 ± 10.4 minutes] and IV [55.7 ± 4.5 minutes]) when compared with control (I [27.0 ± 6.1] and bicarbonate groups (III [29.5 ± 6.6 minutes] and V [26.2 ± 4.2 minutes]), there were no intergroup differences in the onset or duration of analgesia between the tromethamine buffered groups (Fig. 1). Multiple regression analysis revealed that duration was related to both pH and PCO_2. The coefficient of determination for this model was 0.7669. Duration of analgesia predicted with the use of this model was in reasonable agreement with those actually measured (Fig. 3).

Discussion

Davis et al. (10) reported that CO_2 blocked nerve conduction in a dose dependent manner in 1928. Since that report, there have been many studies with regard to the effects of CO_2 and pH on nerve conduction (6,11–13). Catchlove (6) integrated these effects with the action of an incomplete blocking concentration of local anesthetics and concluded that the combination of CO_2 and local anesthetic produced a much more profound block than when these agents were applied separately. Catchlove also reported that these effects reached a maximum at the highest pH

Table 2. Intergroup Comparisons of Local Anesthetic Solutions and Blockade Characteristics

	Group I	Group II	Group III	Group IV	Group V
pH[a]	4.351[c]	7.135[d]	7.134[d]	7.714[e]	7.72[e]
	±0.128	±0.128	±0.031	±0.02	±0.04
PCO₂ (torr)[a]	12.61[c]	2.84[d]	84.99[e]	2.77[d]	114.26[f]
	±2.61	±0.30	±3.35	±0.38	±2.95
Right thoracic level[b]	10	10	10	10	10
	±1.0	±1.0	±1.0	±1.0	±1.0
Left thoracic level[b]	10	10	10	10	10
	±0.5	±1.0	±1.0	±1.0	±0.5
Hypotension (frequency)	0/10	1/10	0/10	0/10	0/10
Motor score[b]	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Specific gravity[a]	1.3384	1.3383	1.3386	1.3384	1.3380
of solution	±0.0005	±0.0012	±0.0005	±0.0005	±0.0004

[a]Mean ± sd; [b]Median ± Quantiles; [cdef]intergroup values for pH or PCO₂ with different letters are significantly different at the $P < 0.001$ level.
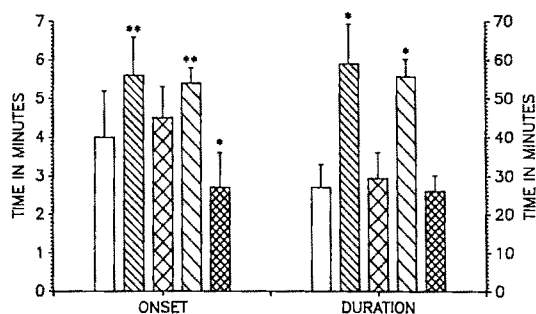
Figure 1. Intergroup differences in onset times and duration of analgesia. Data are presented as mean ± sd. For onset data, * indicates a significantly shorter onset time for Group 5, whereas ** indicates significantly longer onset times for Groups 2 and 4. For the duration data, * indicates significantly longer durations for Groups 2 and 4.

Figure 2. Measured (abcissa) and predicted (ordinate) onset times are presented as open circles. The identity line is provided for reference. Predicted values were calculated according to Onset = $(0.3779 * pH) - (0.0214 * PCO_2) + 2.795$ ($R^2 = 0.51559$).

studied (6) and on the basis of these results proposed that the earliest phase of neural blockade with carbonated local anesthetic solutions is due to rapid diffusion of CO_2 intraneurally. The normal blocking action of local anesthetic then follows that initiated by CO_2. After the CO_2 diffuses across the neural membrane, the pH of the local anesthetic solution remaining in the epidural space increases resulting in an increase in the nonionized (mermeable) form of the local anesthetic. This results in conditions favorable for diffusion trapping (6). The differential effects of CO_2 and pH on nerve conduction have not been demonstrated in the human clinical situation.

The pKa of 2% 2CP is approximately 8.9. With use of the Henderson-Hasselbach equation, it is apparent that the ionized form of plain 2CP is greater than the nonionized form at tissue pH. At a pH of 4.6, the nonionized form of 2CP is 0.01%; at pH 7.1, it is 1.6%; and at pH 7.7, it is 5.9%.

Prior to completing this study, it was believed that the addition of any buffer to 2% 2CP to increase the

pH would hasten the onset of epidural analgesia because no vitro studies have shown that the nonionized form of a local anesthetic passes more readily through nerve membranes than the ionized form (14,15). Our data clearly refute this hypothesis because the two tromethamine solutions buffered to pH 7.1 and 7.7 had significantly longer onset times when compared with the other study solutions. Because there were no significant differences in onset times between the two tromethamine solutions, it appears that there is a minimal dependence on the amount of nonionized drug or pH when considered alone in the pH range of this study. Effects of pH would be expected to be at a maximum at or close to the pKa. Unfortunately this pH range is not achievable with 2CP owing to precipitation of the drug that occurs at pH 8.

On the other hand, our data demonstrate that onset of action of a 2CP solution buffered to a pH of 7.7 with sodium bicarbonate was more rapid in onset
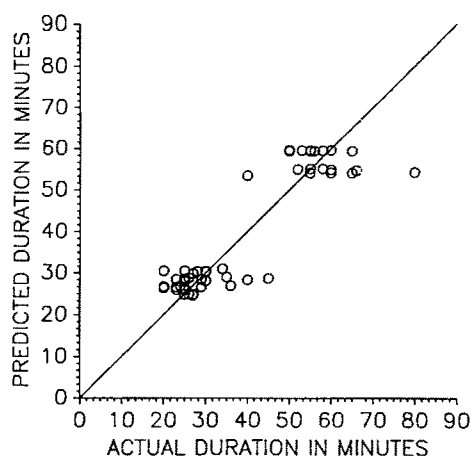
Figure 3. Measured (abcissa) and predicted (ordinate) duration of epidural analgesia are presented as open circles. The identity line is provided for reference. Predicted values were calculated according to Duration = (8.8583 * pH) − (0.29989 * PCO$_2$) − 5.887 (R^2 = 0.81406).

of action than was onset of action of the control solution, the tromethamine buffered solutions, or the solution buffered to a pH of 7.1 with sodium bicarbonate. These data are in excellent agreement with those of Glosten et al. (5) who reported no significant increase in the speed of onset with 2CP solutions adjusted to a pH of 7.08. The PCO$_2$ of the pH adjusted solution of 2CP reported by Glosten et al. was 123.3 ± 31.6 mm Hg and was similar to that of our solution adjusted to pH 7.7 with sodium bicarbonate (114.3 ± 3.0 mm Hg). Because Glosten et al. had an elevated PCO$_2$ at a moderately increased pH and did not observe a difference in onset time it appears that PCO$_2$ is not the sole determinant of onset. Our finding that only the combination of a pH of 7.7 and a PCO$_2$ of 114 torr produced a more rapid onset supports the hypotheses of Catchlove (6), Condouris and Shakalis (13) that a combination of increased CO$_2$ and pH are required to produce shorter onset times. This conclusion is further supported by multiple regression analysis that predicted both pH and PCO$_2$ are related to onset time. One must be cautious, however, because this model only explains 51% of the variance in the data. In addition, when one examines a plot of the predicted versus the measured onset times (Fig. 2), it is apparent that there is a random distribution around the identity line. These findings clearly illustrate that there are additional factors responsible for determining onset time. These additional factors were not identified by the present study. It seems likely that these factors will turn out to be drug related rather than patient related because our within-group coefficients of variation were in the range of 25%. Until these factors are

identified, predictions of optimum pH and/or PCO$_2$ are not possible for other drugs.

Catchlove (12) reported that the effects of CO$_2$ were concentration dependent with a plateau occurring at approximately 9.6%. Further increase in CO$_2$ to 50% caused little additional potentiation. Based on these findings, we would have expected any effects of CO$_2$ to be maximized in the group adjusted to a pH of 7.1 with bicarbonate because the CO$_2$ concentration was approximately 11%. Increasing the pH to 7.7 with bicarbonate increased the CO$_2$ concentration only to approximately 15%.

The longer duration of action that was noted in the two tromethamine buffered groups may be due to the fact that tromethamine molecules do not cross the neural membrane (16). The initial pH of the adjusted solution was maintained for a prolonged period allowing a much higher amount of 2CP to diffuse intraneurally. The longer duration can be explained by the fact that the resultant elevated intraneural drug concentration requires a longer time to dissipate. This hypothesis is supported by the multiple regression analysis that demonstrated that duration was significantly influenced to a large degree by pH and to a lesser degree by PCO$_2$. Approximately 80% of the variance in the data is explained by this model. Reasonable agreement exists when one examines the relationship of the actual and predicted values when plotted using the identity line as a reference (Fig. 3).

Our data differ from those of Parnass et al. (17) who reported that the alkalinization of a local anesthetic could cause an accelerated decrease in blood pressure. Only one patient in our study developed hypotension, which was in the tromethamine buffered group (Group II).

In summary, alterations in onset of action of 2CP appear to involve critical levels of PCO$_2$ and pH in addition to other currently unidentified albeit important factors. Prolongation of epidural analgesia appears to be heavily influenced by changes in pH which, depending on choice of alkalinizing agent, can be fairly long lived. A pH adjustment of 2% 2CP to 7.7 with sodium bicarbonate significantly decreased the onset of epidural analgesia, which under routine circumstances, may not appear to be clinically significant. However, a more rapid onset of analgesia with the use of buffered 2CP could be of benefit to both the mother and fetus in cases where an emergency forceps delivery must be performed or in instances in which imminent delivery is anticipated. The increased duration of action of tromethamine buffered 2% 2CP is clinically significant, but this benefit must be weighed against the slower onset of action. Additional well controlled prospective studies

are warranted to determine whether 1) other factors governing speed of onset can be identified, and 2) whether the data reported here for 2CP can be reproduced with other local anesthetics.

References

1. DiFazio CA, Carron H, Grosslight KR, Moscicki JC, Bolding WR, Johns RA. Comparison of pH adjusted lidocaine solutions for epidural anesthesia. Anesth Analg 1986;654:760–4.

2. Douglas MJ, McMorland GH, Jeffery WK, et al. The effect of pH adjustment of bupivacaine on epidural anesthesia for cesarean section (abstr). Anesthesiology 1986;65:A380.

3. Hilgier M. Alkalinization of bupivacaine for brachial plexus block. Reg Anaesth 1985;10:59–61.

4. Redick LF. pH adjustment of chloroprocaine solutions (letter). Anesth Analg 1987;66:286.

5. Glosten B, Dailey PA, Preston PG, et al. pH-Adjusted 2-chloroprocaine for epidural anesthesia in patients undergoing postpartum tubal ligation. Anesthesiology 1988;68:948–50.

6. Catchlove RFH. The influence of CO_2 and pH on local anesthetic action. J Pharmacol Exp Ther 1972;181:298–309.

7. Raj PP, Ohlweiler D, Hitt BA, Denson DD. Kinetics of local anesthetic esters and the effects of adjuvant drugs on 2-chloroprocaine hydrolysis. Anesthesiology 1980;53:307–14.

8. Crawford TS. Principles and Practice of Obstetric Anesthesia. Oxford: Blackwell Scientific Publications, 1984:232.

9. Bromage PR. Epidural Analgesia. Philadelphia: WB Saunders, 1978:144.

10. Davis H, Pascual W, Rice LH. Quantitative studies of the nerve impulse III: The effect of carbon dioxide on the action current of modulated nerve. Am J Physiol 1928;86:706–24.

11. Hettwer JP. The relation of threshold of excitability of nerve to carbon dioxide tension. Am J Physiol 1938;122:275–80.

12. Catchlove RFH. Potentiation of two different local anaesthetics by carbon dioxide. Br J Anaesth 1973;45:471–4.

13. Condouris GA, Shakalis A. Potentiation of the nerve depressant effects of local anaesthetics by carbon dioxide. Nature 1964;204:57–9.

14. Ritchie TM, Ritchie B, Greengard P. The effect of the nerve sheath on the action of local anesthetics. J Pharmacol Exp Ther 1965;150:160–4.

15. Cohen EN, Levine DA, Coliss JE, Gunther RE. The role of pH in the development of tachyphylaxis to local anesthetic agents. Anesthesiology 1968;29:994–1001.

16. Nahas GG. The pharmacology of tris(hydroxymethyl)aminomethane (THAM): Pharmacol Rev 1962;14:447–72.

17. Parnass SM, Carron MJ, Becker GL. Incidence of hypotension associated with epidural anesthesia using alkalinized and nonalkalinized lidocaine for cesarean section. Anesth Analg 1987;66:1148–50.

Halogenation and Anesthetic Potency

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TARG AG, YASUDA N, EGER EI II, HUANG G, VERNICE GG, TERRELL RC, KOBLIN DD. Halogenation and anesthetic potency. Anesth Analg 1989;68:599–602.

Previous studies have shown that the anesthetic potency of organic compounds increases as a given halogen is replaced with successively larger halogens. These studies often are limited in the accuracy of determination of potency, rarely correlate potency with physical properties, and usually fail to include ether compounds. Because establishing relationships between structure and activity may shed light on anesthetic action, we studied the new anesthetic, I-537 (CHF_2-O-CHBr-CF_3), relative to two other ether anesthetics, I-653 (CHF_2-O-CHF-CF_3) and isoflurane (CHF_2-O-CHCl-CF_3) for both of which MAC and oil/gas partition coefficients are accurately known. The oil/gas partition coefficient of I-537 at 37°C was found to be 245 ± 6 (mean ± SD) and the MAC in Sprague-Dawley rats 0.52 ± 0.07%. Increasing atomic weight of the 1-ethyl halogen (i.e., F in I-653, Cl in isoflurane, and Br in I-537) progressively decreases MAC (increases potency) and increases lipid solubility. Although potency and solubility change by more than 10-fold, the product of MAC and the oil/gas partition coefficient remains essentially constant (120 ± 11). However, this product is significantly less than that for other inhaled anesthetics, a finding which either challenges the unitary theory of narcosis or suggests that the lipid solvent classically used to model the site of anesthetic action (olive oil) is inappropriate.

Key Words: POTENCY, ANESTHETIC—MAC, inhalation anesthetics. ANESTHETICS, VOLATILE—isoflurane, I-653, I-537. THEORIES OF ANESTHETIC ACTION, LIPID SOLUBILITY. PHYSICS, SOLUBILITY.

Structure-activity relationships may provide insights into the mechanisms of anesthetic action. Results from previous studies suggest that halogenation of an organic compound with bromine (Br) produces a more potent anesthetic than halogenation with chlorine (Cl) which, in turn, provides greater potency than fluorine (F) (1,2). Thus, in the CF_3CH_2X series (where X indicates the halogen), substitution of Br for Cl has been reported as increasing potency nearly 3-fold while substitution of Cl for F has been said to increase potency 5-fold (1,2). This relationship also has been reported with other alkane series (Fig. 1).

However, these findings are qualified by: 1) limited accuracy in the determination of anesthetic potency; 2) absence of attempts to correlate potency with physical properties (e.g., important physical characteristics such as lipid solubility are unknown or inadequately defined); and 3) failure to evaluate ether compounds. Only one oil/gas partition coefficient is available for the CF_3-CHFX [namely CF_3-CHFBr (7)] and CF_3-CHClX [namely CF_3-CHClBr (8)] series, and only two are available for the CF_3-CHBrX [CF_3-CHBrF (7) and CF_3-CHBrCl (8)] and CF_3CH_2X [CF_3CH_2F (2) and CF_3CH_2Cl] [Fiserova-Bergerova V, Kawiecki R, unpublished data (9)] series. The noble gases, Ar, Kr, and Xe, are the only series for which all oil/gas partition coefficients have been determined (Table 1).

We have investigated the properties of a new brominated ether anesthetic, (I-537: CHF_2-O-CHBr-CF_3), and compared them to those of two other previously documented ether compounds, one containing chlorine (isoflurane: CHF_2-O-CHCl-CF_3) and the other containing fluorine (I-653: CHF_2-O-CHF-CF_3).

INCREASING HALOGEN OR NOBLE GAS SIZE
DECREASES THE ANESTHETIC ED_{50}

ED_{50}'s NORMALIZED TO ED_{50} FOR Br OR Kr

Figure 2. This schematic representation of the closed circuit used in the study is described in detail in the text.
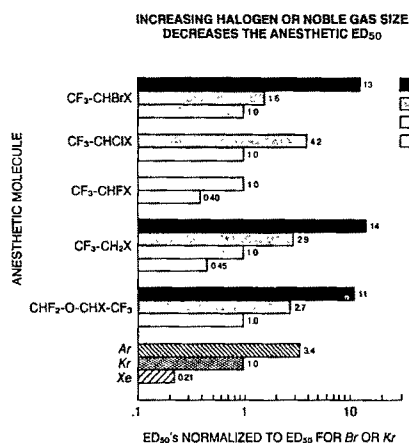
Figure 1. ED_{50} values for F, Cl, Br, and I (all indicated by X) are normalized to ED_{50} for Br; ED_{50} values for Ar, Kr, and Xe are normalized to ED_{50} for Kr. Ne, Ar, Kr, and Xe share rows in the periodic table of the elements with F, Cl, Br, and I respectively. Ne results in no anesthesia in tolerable pressure ranges. The following ED_{50} references are not normalized. They are reported by species and methods of ED_{50} determination and ED_{50} (in % atm): CHF_2-O-CHF-CF_3 (rat; no movement with supramaximal stimulus; 5.72%) (3); CHF_2-O-CHCl-CF_3 (rat; no movement with supramaximal stimulus; 1.38%) (4); CF_3-CH_2F (unspecified species and endpoint; 40%) (2); CF_3-CH_2Cl (mouse; loss of righting reflex; 8%) (1); CF_3-CH_2Br (mouse; loss of righting reflex; 2.8%) (1); CF_3-CH_2I (mouse; loss of righting reflex; 1.25%) (1); CF_3-CHFBr (unspecified species and endpoint; 5%) (2); CF_3-CHFI (unspecified species and endpoint; ~2%) (2); CF_3-$CHCl_2$ (mouse; loss of righting reflex; 2.7%) (1); CF_3CHClBr (mouse; loss of righting reflex; 0.65%) (5); CF_3-$CHBr_2$ (mouse; loss of righting reflex; 0.4%) (1); Ar (mouse; loss of righting reflex; 1520%) (6); Kr (mouse; loss of righting reflex; 450%) (6); and Xe (mouse; loss of righting reflex; 95%) (6). Accuracy of ED_{50} values from earlier studies may be limited, because these studies did not control for temperature changes likely to have occurred during measurement of the anesthetic endpoints.

Table 1. Noble Gas Series

Noble gas	ED_{50} (% atm)	O/G	ED_{50} x O/G
He	† (10, 11)	0.0176 (12)	†
Ne	† (11)	0.0217 (12)	†
Ar	1520 (6)	0.150 (12)	228
Kr	450 (6)	0.458 (13)	206
Xe	95 (6)	1.85 (13)	176

O/G is the oil/gas partition coefficient at 37°C, the oil being olive oil.
ED_{50} for this series was the righting reflex.
†Anesthetic effects of He and Ne are antagonized by the high pressures required to obtain the theoretically anesthetizing concentration.
Numbers in parentheses indicate reference for the value.

Materials and Methods

Partition Coefficients

We determined oil/gas (N = 6) and blood/gas (N = 4) partition coefficients of I-537 by standard techniques using olive oil as the lipid solvent (14,15). Blood was obtained from fasting, preoperative patients after acquiring informed consent and approval from the UCSF Committee on Human Research.
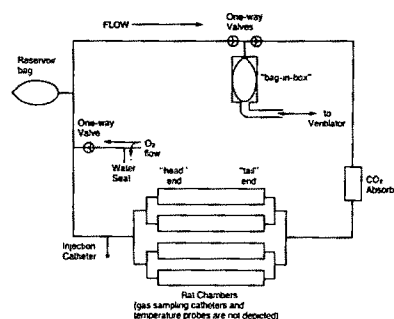
MAC

Our study was approved by the UCSF Committee on Animal Research. Eight specific-pathogen-free, 2.5-month-old, male Sprague-Dawley rats weighing 315 ± 20 g (mean ± SD) were purchased from the Charles River Laboratories. Animals were caged individually and each had continuous access to standard rat chow and tap water before and after study.

MAC was determined as described previously (4,16), except that our limited supply of I-537 required the use of a closed anesthetic system. We modified a system used earlier (17), using a circuit (Fig. 2) rather than a to-and-fro system for elimination of carbon dioxide. We used Plexiglas® cylinders (chambers) 30 cm long, with an internal diameter of 6.3 cm, to house the rats during individual study (one rat per chamber). This diameter permitted the rat to crawl into the chamber, but prevented his turning around.

Both ends of the chamber were equipped with rubber stoppers. The stopper at the "head" end of the chamber was traversed by two tubes: a catheter (not shown in Fig. 2) for sampling the atmosphere in the chamber, and a universal adapter connected to the circuit tubing for recirculation of gas containing I-537. The sampling catheter was sealed with a stopcock when not in use. Four chambers were connected in parallel with two tiers of T-tubes. The resulting single outflow tube had a catheter inserted (sealed with a stopcock when not in use) for injecting anesthetic vapor. The outflow tube was connected to a T-tube. One arm of the T-tube was connected via a one-way valve (allowing only ingress of oxygen) to an oxygen source equipped with a low-pressure, water-controlled, pop-off valve. The other end of the T-tube was connected to another T-tube fitted with a reservoir bag. The system was connected to a bag-in-box to which an Air-Shields® Ventimeter Ventilator intermittently (20–30 times per minute) applied positive pressure. The bag had a nominal volume of 500 ml. This arrangement incorporated two one-way valves and provided the circulatory movement of gases in

the system needed to eliminate carbon dioxide and to assure adequate mixing of anesthetic introduced into the system. A carbon dioxide absorber charged for each study with 50–55 g of fresh, commercial (Sodasorb®) soda lime was placed between the ventilator and the "tail" end of the chamber. The absorber had walls of stainless-steel mesh and fit snugly within a surrounding Plexiglas® housing.

The stopper at the "tail" end of each of the chambers was pierced by two holes, one for the tail and one through which a small rectal temperature probe was passed (not shown in Fig. 2), and by a universal adapter connected to the circuit tubing by two tiers of T-tubes. This design allowed us to flush oxygen through the circuit before beginning the study and to circulate I-537 during the study. I-537 in oxygen flowed through the chamber from "tail" to "head" end. The hole for the tail was large enough to allow passage of the tail, snugly but without constriction.

We placed one rat in each chamber and inserted rectal thermister probes which we secured to the tails with tape. The tail was pulled through the hole in the stopper which was then sealed with Teflon® stopcock grease. Rectal temperatures were kept between 37.2–39.0°C by external heating (infrared lamps) or cooling (ice applied to the tube). A minimum of 1 L·min^{-1}·rat^{-1} flow of 100% oxygen was directed through the circuit for at least 15 minutes after which all openings to the circuit were sealed except that for oxygen delivery.

A gaseous mixture of I-537 (vapor pressure = 175 mm Hg at 20°C, Vernice GG, personal communication) was produced by adding 0.01–0.10 ml liquid I-537 to 10–30 ml of oxygen in a 50-ml glass syringe sealed with a stopcock. The evaporation of the I-537 rapidly increased the volume in the syringe. Anesthesia was induced smoothly in each rat by adding vapor to the circuit through the injection catheter. MAC was determined in duplicate in all rats.

MAC was measured using a variation of previously described techniques (4,16). The rats were studied in two sets of four, within the same day. At least 20 minutes were allowed for equilibration at each step (concentration) used to bracket MAC. Because we found that I-537 had a relatively high blood solubility (blood/gas partition coefficient, 3.22 ± 0.10, mean ± SD), we ensured approximate equilibration between inspired gas (which we measured) and alveolar gas (which we did not measure) by applying a supramaximal stimulus to the tail at step-wise decrements in concentrations, beginning with a concentration that exceeded MAC by two or more steps. The process was repeated once in each rat. The duration

of anesthesia prior to reaching the first concentration permitting movement was 119 ± 11 minutes.

The circulating concentrations of I-537 and carbon dioxide were monitored by intermittent sampling. At 2-minute intervals, gas samples were drawn from one of the compartments' sampling catheters into a 50-ml glass syringe sealed with a stopcock. The constancy of I-537 concentration at each step was determined with a Beckman LB-2 infrared halothane analyzer. Gas samples were drawn for carbon dioxide analysis (Beckman LB-2 carbon dioxide analyzer) every 1–2 hours. The concentration of carbon dioxide within the circuit remained between 0.7–0.8%. The halothane analyzer was calibrated with I-537 samples from a secondary tank standard that had been calibrated with a primary standard produced by injection of a liquid aliquot of I-537 into a flask of known volume. The determination of the primary standard required the determination of the specific gravity of I-537 (1.85 g/ml at 22°C).

Infrared analysis was used only for the monitoring needed to assure constancy of the anesthetic concentration. We used gas chromatography to determine the concentrations applied to the estimate of MAC. Sixty seconds prior to each MAC determination, a sample was drawn from one of the compartments' sampling catheters and injected into a Gow Mac Model 750 gas chromatograph equipped with a 30-m, fused silica open tubular capillary column (0.53 mm inside diameter) coated with a 5-μm layer of methyl-silicone oil (J & W Scientific DB-1) maintained at 40°C. A nitrogen carrier stream of 20 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 45 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop. The chromatograph was calibrated with the secondary tank standard prior to each sample concentration determination.

Results

The blood/gas and oil/gas partition coefficients of I-537 at 37°C were 3.22 ± 0.10 and 245 ± 6 (means ± SD). The MAC of I-537 was 0.52 ± 0.07%. All rats survived and appeared healthy 72 hours after anesthesia.

Discussion

Anesthetic potency increased 4.1-fold when chlorine (isoflurane) replaced fluorine (I-653), and 2.7-fold when bromine (I-537) replaced chlorine. Our results

Table 2. CHF_2-O-CHX-CF_3 Series

X	MAC (% atm)	O/G	MAC x O/G
F (I-653)	5.72 (3)	18.7 (18)	107
Cl (Isoflurane)	1.38 (4)	90.8 (19)	125
Br (I-537)	0.52	245	127

O/G is the oil/gas partition coefficient at 37°C, the oil being olive oil. Numbers in parentheses indicate reference for the value.

in this ether series confirm those for series of alkanes and are similar to anesthetic potency changes observed with the noble gases (Fig. 1). Combined, such findings indicate that anesthetic potency increases consistently with increasing molecular weight (Fig. 1). This effect of increasing weight (and/or change in associated physical properties) must be accounted for by any theory of narcosis and may be applicable to the design of new anesthetics.

The increase in potency due to halogen substitution correlated closely with increased lipid (olive oil) solubility (Table 2), a finding consistent with the perception that anesthetics act in some hydrophobic site within the brain (20). The mean product of MAC and the respective oil/gas partition coefficient for I-653, isoflurane, and I-537 was 120 ± 11. However, this product is significantly less than the values reported for other inhaled anesthetics. For example, the mean product of MAC and the respective oil/gas partition coefficient for methoxyflurane ($CHCl_2$-CF_2-O-CH_3), halothane (CF_3-CHBrCl), fluroxene (CF_3-CH_2-O-CH=CH_3), and cyclopropane [$(CH_2)_3$] is 238 ± 26 (21,22). Because methoxyflurane and fluroxene are ethers, the difference in product between these four anesthetics and the three evaluated in the present study is not simply a consequence of the ether structure. In other species (mice, humans, and dogs), enflurane (CHF_2-O-CF_2-CHFCl, a structural isomer of isoflurane) has a MAC approximately 50% greater than isoflurane despite the near-identity of their solubilities in olive oil (5,22). If the unitary theory of narcosis applies to I-653, isoflurane, and I-537, it appears that olive oil is not entirely representative of the anesthetic site of action. Discovery of a more representative solvent may provide further insights into the character of the site of anesthetic action. Alternatively, one might argue that the unitary theory of narcosis is incorrect.

References

1. Robbins BH. Preliminary studies of the anesthetic activity of fluorinated hydrocarbons. J Pharmacol Exp Ther 1946;86:197–204.

2. Larsen ER. Fluorine compounds in anesthesiology. In Tarrant P ed., Fluorine chemistry reviews. New York and London: Marcel Dekker, Inc., 1969:17.

3. Eger EI II, Johnson BH. MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. Anesth Analg 1987;66:974–6.

4. White PF, Johnston RR, Eger EI II. Determination of anesthetic requirement in rats. Anesthesiology 1974;40:52–7.

5. Deady JE, Koblin DD, Eger EI II, Heavner JE, D'Aoust B. Anesthetic potencies and the unitary theory of narcosis. Anesth Analg 1981;60:380–4.

6. Miller KW, Paton WDM, Smith EB, Smith RA. Physicochemical approaches to the mode of action of general anesthetics. Anesthesiology 1972;36:339–51.

7. Edelist G, Singer MM, Eger EI II. Solubility of Teflurane in various biological media. Anesthesiology 1964;25:223–25.

8. Larson CP, Eger EI II, Severinghaus JW. The solubility of halothane in blood and tissue homogenates. Anesthesiology 1962;23:349–55.

9. Fiserova-Bergerova V. Gases and their solubility: a review of fundamentals. In Fiserova-Bergerova V, ed., Modeling of inhalational exposure to vapors: uptake, distribution, and elimination, Vol. I. Boca Raton, Florida: CRC Press, 1983:20.

10. Miller KW, Wilson MW, Smith RA. Pressure resolves two sites of action of inert gases. Mol Pharmacol 1978;14:950–9.

11. Lever MJ, Miller KW, Paton WDM, Smith EB. Pressure reversal of anaesthesia. Nature 1971;231:368–71.

12. Battino R, Evans FD, Danforth WF. The solubilities of seven gases in olive oil with reference to theories of transport through the cell membrane. J Amer Oil Chem Soc 1968;45:830–3.

13. Yeh S-Y, Peterson RE. Solubility of carbon dioxide, krypton, and xenon in lipids. J Pharm Sci 1963;52:453–8.

14. Lerman J, Willis MM, Gregory GA, Eger EI II. Osmolarity determines the solubility of anesthetics in aqueous solutions at 37°C. Anesthesiology 1983;59:554–8.

15. Tanifuji Y, Eger EI II, Terrell RC. Some characteristics of an exceptionally potent inhaled anesthetic: thiomethoxyflurane. Anesth Analg 1977;56:387–90.

16. Fassoulaki A, Eger EI II. Piracetam does not change the anaesthetic requirement for halothane. Br J Anaesth 1985;57:1110–2.

17. Eger EI II, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. Anesth Analg 1987;66:977–82.

18. Eger EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 1987;66:971–3.

19. Koblin DD, Eger EI II, Johnson BH, Collins P, Harper MH, Terrell RC, Speers L. Minimum alveolar concentrations and oil/gas partition coefficients of four anesthetic isomers. Anesthesiology 1981;54:314–7.

20. Meyer KH. Contributions to the theory of narcosis. Trans Faraday Soc 1937;33:1062–8.

21. Cullen DJ. Anesthetic depth and MAC, In Miller RD, ed., Anesthesia, 2nd ed. New York, Churchill Livingston, 1986:558.

22. Eger EI II. Uptake of inhaled anesthetics: the alveolar to inspired difference. Anesthetic uptake and action. Baltimore: Williams and Wilkins, 1974:82.

The Effect of Advancing Age on the Sympathetic Response to Laryngoscopy and Tracheal Intubation

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BULLINGTON J, MOUTON PERRY SM, RIGBY J, PINKERTON M, ROGERS D, LEWIS TC, PREGANZ P, WOOD AJJ, WOOD M. The effect of advancing age on the sympathetic response to laryngoscopy and tracheal intubation. Anesth Analg 1989;68:603–8.

The effect of aging on the hemodynamic and sympathetic response to tracheal intubation was evaluated in 27 patients aged 18 to 80 years, ASA Class I and II, given atropine 0.4 mg and diazepam 10 mg as premedication and thiopental, 4.0 mg/kg, and succinylcholine 100 mg for anesthesia induction. Laryngoscopy and tracheal intubation was performed 60 seconds after induction. The elderly had significantly less chronotropic response to intubation 2, 3, 4, and 5 minutes after induction so that the maximum increase in heart rate above awake values was negatively correlated with age ($R = -0.66$, $P < 0.001$). Baseline systolic blood pressure (SBP) and mean BP increased significantly with age ($R = 0.81$, $P < 0.001$ and $R = 0.76$, $P < 0.001$, respectively) but age was not significantly related to increases in SBP and mean BP following intubation. Baseline plasma norepinephrine (NE) levels increased with age ($R = 0.51$, $P < 0.01$). Following intubation, mean plasma NE concentrations were significantly higher in elderly patients than young patients, despite the diminished heart rate response. Heart rate (HR) per pg/ml of NE, a measure of cardiac sensitivity to beta stimulation, was therefore significantly less 2, 3, and 4 mins after induction in elderly patients than in younger patients. To determine if this alteration in cardiac sensitivity to endogenous catecholamines was reflected by changes in beta receptor function on lymphocytes, beta receptor density and the proportion of receptor binding agonist with high affinity (%RH) were measured. No significant correlation between beta-receptor affinity for agonist, %RH, or receptor density was found with age, HR, or HR per pg/ml NE. Our results indicate that the elderly have a significantly lower chronotropic response to intubation than do the young. As plasma catecholamines were higher in the elderly, while the blood pressure rise was not different, we conclude that this loss of response is probably not due to diminished sympathetic response or baroreceptor function. However, we were not able to correlate the heart response to norepinephrine with direct measures of beta₂ receptor function on circulating lymphocytes.

Key Words: AGE—cardiovascular system. INTUBATION, TRACHEAL—vascular responses. ANESTHETIC TECHNIQUES—laryngoscopy. SYMPATHETIC NERVOUS SYSTEM—catecholamines, norepinephrine. RECEPTORS, ADRENERGIC—beta₂.

Laryngoscopy and tracheal intubation are often associated with hypertension, tachycardia, and an increase in plasma catecholamine concentrations (1–3). The mechanism for these reflex cardiovascular changes is unknown, but they may be a result of reflex sympathetic activation, perhaps involving the baroreceptor system, provoked by stimulation of the epipharynx and laryngopharynx. Reflex cardiovascular responses to mechanical stimulation of the upper airway have been described in cats (4) when increased neuronal activity was observed in cervical sympathetic efferent fibers. It has been suggested that the pressor response to tracheal intubation is also secondary to a reflex sympathetic discharge in humans since plasma catecholamine concentrations are elevated following tracheal intubation, and beta adrenergic receptor blockade attenuates the response (5–7).

An exaggerated response to laryngoscopy accompanied by a marked increase in plasma norepinephrine concentrations has been reported in hypertensive subjects (8). The incidence of hypertension and ischemic heart disease is increased in the elderly (9,10); in addition, important changes occur in the autonomic nervous system with advancing years. The baroreceptor response to hypertension is diminished (11) and the elderly are less sensitive to beta-adrenergic agonists and antagonists as a consequence of reduced affinity of the beta-receptor for adrenergic agonists (12,13). Thus, patients in older age groups may show altered hemodynamic and sympathetic responses to the stimulus of laryngoscopy and tracheal intubation. The purpose of the present study was to determine the effect of increasing age on the adrenergic response to tracheal intubation and to evaluate the mechanism for any changes found.

Methods

The study was approved by the Vanderbilt Committee for the Protection of Human Subjects and all patients gave written informed consent prior to participation in the study. Twenty-seven patients, aged 18 to 80 years, ASA physical status I or II, were studied. Patients receiving any preoperative therapeutic cardiovascular medications were excluded from the study and no patient had recognized cardiovascular disease; in particular, patients with ischemic heart disease or hypertension by history or examination were excluded from the study. All patients rested in the hospital the night before surgery and remained supine during this period and up to arrival in the holding room.

Premedication consisted of diazepam, 10 mg, orally and atropine, 0.4 mg intramuscularly 60 min before induction of anesthesia. Following awake baseline recordings of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR), general anesthesia was induced with thiopental, 4.0 mg/kg followed by succinylcholine, 100 mg. Blood pressure was measured using an automated blood pressure cuff and heart rate was measured from the electrocardiogram. SBP, DBP, and HR were recorded after thiopental but before succinylcholine (zero time) and 1, 2, 3, 4, and 5 minutes after induction. Laryngoscopy and tracheal intubation were performed 60 seconds after induction.

Venous blood samples were drawn with the patients awake (baseline) and 2, 3, and 4 minutes after induction for the measurement of plasma norepinephrine concentrations by a radioenzymatic assay

(14). Blood samples for measurement of norepinephrine were taken into tubes (on ice) containing reduced glutathione. At the same time as the blood samples were drawn, each patient's heart rate and blood pressure were recorded as described above. Venous blood (45 ml) was drawn from patients when in the holding room before anesthesia had commenced for the measurement of beta-receptors on lymphocytes.

A radioligand binding technique using [125]iodopindolol was used to determine receptor density and the receptor affinity for agonists was determined from isoproterenol competition binding curves (15).

Whole blood was drawn and added to pre-chilled polypropylene tubes containing EDTA (1.4 mg/ml blood). Following centrifugation at 250 g for 20 minutes the platelet-rich plasma was removed and the buffy coat collected and diluted with phosphate-buffered saline (pH 7.6) containing 3 mM EDTA. Mononuclear leukocytes were isolated according to the method of Boyum (16). The MNL band (80–90% lymphocytes) was harvested and resuspended in 90 mM NaCl, 15 mM $MgCl_2$, 3 mM EDTA, and 6 mM sucrose buffered with 20 mM Tris-HCl (pH 7.6 at 37°C, Vol = 35 ml) and centrifuged at 38000g for 10 min at 4°C. The pellet was resuspended in 2 mM Tris-HCl containing 3 mM EDTA (Vol = 4 ml), homogenized for 10 seconds (Brinkman Polytron; setting 7) and recentrifuged at 38,000g for 10 minutes at 4°C. The final pellet was resuspended in Buffer A containing 20 mM Hepes (pH 7.4), 100 mM NaCl, 25 mM $MgCl_2$, and 3 mM EDTA and homogenized for 10 seconds (setting 5) before freezing in an ethanol-dry ice bath. Membranes were stored at −76°C. Before use membranes were thawed and homogenized for 5 sec (setting 5) and then diluted to an appropriate protein concentration with Buffer A.

Lymphocyte membranes were incubated with ^{125}I-iodopindolol for 60 min at 37°C in a final volume of 250 μl containing 12 mM Tris-HCl (pH 7.6 at 37°C), 60 mM NaCl, 9 mM $MgCl_2$, 1.8 mM EDTA, 3.6 mM sucrose with 4 μg/ml bovine serum albumin and 0.5 mM ascorbic acid. The reaction was stopped by adding 10 ml ice-cold wash buffer, containing 10 mM Tris-HCl, 90 mM NaCl, 15 mM $MgCl_2$, and 3 mM EDTA, and rapidly filtered through Whatman GF/C filter. Filters were washed with a further 10 ml buffer and the radioactivity retained on the filters was determined in a Beckman Gamma 5500 counter at 70% efficiency. Specific binding was calculated as the difference in the amount of I-PIN bound in the absence and presence of isoproterenol (0.1 mM). β-Adrenergic receptor density (B_{max}) was assessed from saturation binding curves by incubating membranes with nine concentrations of I-PIN (5–300 pM).
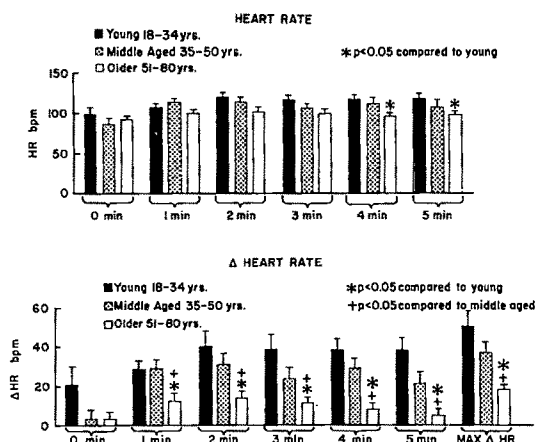
Figure 1. Heart rate and increases in heart rate above awake values (ΔHR) following laryngoscopy and tracheal intubation in young, middle aged and older patients.

Figure 2. Maximum change in heart rate after induction following laryngoscopy and tracheal intubation plotted against age.

Figure 3. Systolic blood pressure and increase in systolic blood pressure above awake values (ΔSBP) following laryngoscopy and tracheal intubation in young, middle aged, and older patients.

The B_{max} was determined from the data using the computer program LIGAND (17).

Receptor affinity for agonist was determined from agonist competition binding studies as previously described (15). Membranes were incubated with I-PIN (20 pM) and isoproterenol (0.1 nM–0.1 mM) in the absence and presence of GppNHp (0.1 mM). Binding curves were analyzed by non-linear weighted regression analysis using LIGAND (17) to determine the best fit of the data to a one vs two affinity state model. For the two affinity state model, estimates were provided by the computer of the association constants for the high (KH) and low affinity states (KL) and the percentage of receptors in the high affinity state (%RH).

Protein concentration was determined by the method of Lowry et al. using bovine serum albumin as a standard (18).

Statistical analysis was by linear regression or analysis of variance followed by non-paired Student's t-test as appropriate.

Results

Figure 1 shows the mean resting heart rate and increase in heart rate above baseline values following induction in the patients studied. Although there was no correlation between resting heart rate and age in patients while awake, linear regression analysis relating increase in heart rate to age showed that the elderly patients had significantly less heart rate response to laryngoscopy and intubation 2 minutes (R = -0.60, P < 0.001), 3 minutes (R = -0.59, P < 0.001), 4 minutes (R = -0.67, P < 0.001), and 5 minutes (R = -0.70, P < 0.001) after induction. The

maximum increase in heart rate above awake baseline values in the post-induction period was also negatively correlated with age (R = -0.66, P < 0.001; Fig. 2). These data indicate that elderly patients have a smaller increase in heart rate than do younger subjects during laryngoscopy and tracheal intubation.

There was a significant correlation between age and baseline SBP (R = 0.81, P < 0.001), DBP (R = 0.55, P < 0 005) and mean blood pressure (R = 0.76, P < 0.001) respectively, showing the expected increase in blood pressure with advancing years (Fig. 3). Age, however, was not significantly related to the increases in SBP, DBP, or mean BP above baseline values that occurred following laryngoscopy and tracheal intubation. When the patients were divided into three groups, young (18–34 yr, N = 9), middle aged (35–50 yr, N = 8), and older (51–80 yr, N = 10), the increases in SBP, DBP, or mean BP above awake values were not significantly different between the groups (Figures 3–5). Thus, elderly patients do not appear to have a greater increase in blood pressure than do younger subjects in response to laryngoscopy and tracheal intubation.
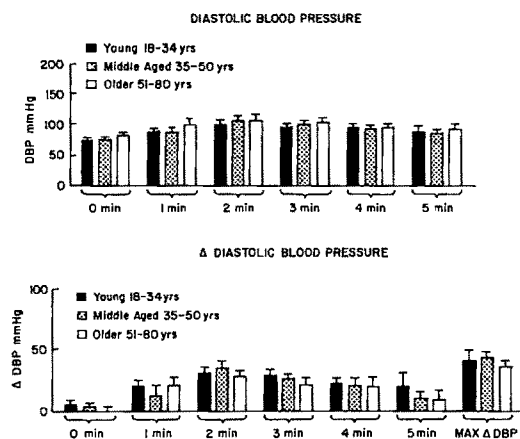
Figure 4. Diastolic blood pressure and increase in diastolic blood pressure above awake values (ΔDBP) following laryngoscopy and tracheal intubation in young, middle aged, and older patients.
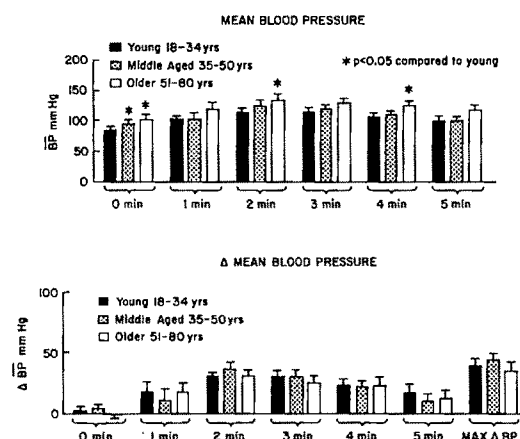
Figure 5. Mean blood pressure and increase in mean blood pressure above awake values (ΔBP) following laryngoscopy and tracheal intubation in young, middle aged, and older patients.

Plasma norepinephrine concentrations in awake patients increased with age ($R = 0.51$, $P < 0.01$). Following intubation, mean plasma norepinephrine concentrations were significantly higher in older patients than in young patients (Fig. 6). The maximum increase in plasma norepinephrine concentration above awake values was also greater in elderly patients, despite their diminished heart rate response (Fig. 7). Thus, in spite of the higher norepinephrine response to laryngoscopy and tracheal intubation, the elderly had a smaller increase in heart rate. HR per pg/ml of norepinephrine, a measure of cardiac sensitivity to beta receptor stimulation, was therefore significantly less 2, 3, and 4 min after induction in older than in younger patients (Table 1).

To determine if this alteration in cardiac sensitivity to endogenous norepinephrine was reflected by changes in beta-receptor function on lymphocytes, beta-receptor density and the proportion of receptors
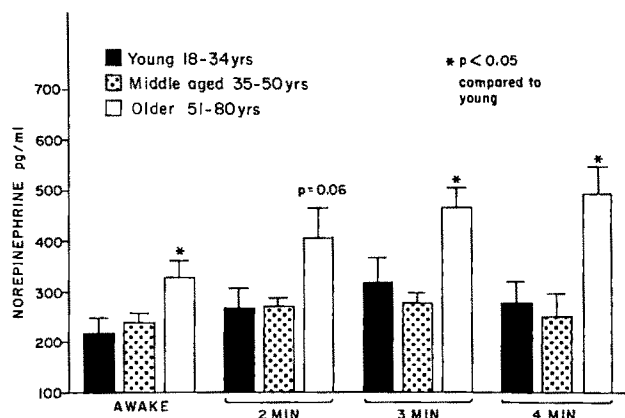
Figure 6. Mean plasma norepinephrine concentrations in young, middle aged, and older patients.

* p<0.05 compared to middle aged
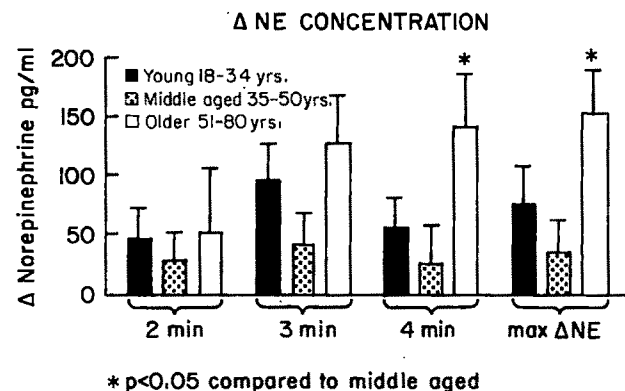
Figure 7. Increase in mean plasma norepinephrine concentrations in young, middle aged, and older patients.

Table 1. Cardiac Sensitivity to Endogenous Norepinephrine

	Heart Rate per pg/ml Plasma Norepinephrine		
	Young (18–34 years)	Middle Aged (35–50 years)	Older (51–80 years)
HR/NE 2 min	0.54 ± 0.10	0.44 ± 0.03	0.29 ± 0.04*
HR/NE 3 min	0.46 ± 0.12	0.39 ± 0.04	0.23 ± 0.03*
HR/NE 4 min	0.51 ± 0.09	0.53 ± 0.13	0.22 ± 0.03*

*$P < 0.05$ compared to young patients.

binding agonist with high affinity (% RH) were measured. Receptor density was 23.9 ± 4.9, 18.5 ± 3.3, 25.1 ± 3.3 fmol/mg protein in young, middle aged, and older subjects, respectively. There was also no significant difference in % RH between any of the three study groups; 39.7 ± 4.3, 46.7 ± 6.2, and 40.6 ± 2.4, respectively (Table 2). In addition, no significant correlation between beta-receptor affinity for agonist (% RH) or receptor density was found with age, HR, increase in HR, or HR per pg/ml of norepinephrine.

Table 2. Beta Receptor Function

	Young 18–34 years	Middle Aged 35–50 years	Older 51–80 years
Receptor density (fmol/mg protein)	23.9 ± 4.9	18.5 ± 3.3	25.1 ± 3.3
% RH	39.7 ± 4.3	46.7 ± 6.2	40.6 ± 2.4

Discussion

Intact autonomic nervous system reflexes and hormonal mechanisms are important in the short term regulation of blood pressure during anesthesia in order to regulate an appropriate response to both hypo- and hypertension. We have previously shown that during sodium nitroprusside-induced hypotension, the elderly exhibit a smaller increase in heart rate than do young patients in spite of similar increases in plasma catecholamine concentrations (19). In the present study we have investigated the hemodynamic and sympathetic response of elderly patients to the "stress" of laryngoscopy and tracheal intubation. We found that plasma norepinephrine concentrations were significantly higher in older patients than young patients and that the maximum increase in plasma norepinephrine concentration above awake resting values was also greater in elderly patients following laryngoscopy and tracheal intubation. In addition, the increase in blood pressure was similar in all age groups. However, despite the higher plasma norepinephrine concentrations in elderly patients, there was a marked difference in the degree of tachycardia associated with the sympathetic stimulation induced by laryngoscopy and tracheal intubation.

The failure of heart rate to increase normally in elderly patients in response to the increase in plasma norepinephrine associated with intubation could be due to either a loss of sensitivity to cardiac beta adrenergic stimulation, so that similar catecholamine levels produced a smaller rise in pulse rate, or to increased baroreceptor sensitivity in the elderly producing, through vagal stimulation, a greater reduction in heart rate in the elderly. An increased baroreceptor sensitivity seems unlikely to be the explanation as previous studies of baroreceptor function in the elderly have shown a decreased rather than increased sensitivity in this age group (11). On the other hand, decreased response to exogenously administered beta receptor agonists has previously been demonstrated in the elderly (12). Thus, the sympathetic stimulation produced by laryngoscopy and tracheal intubation produces similar increases in blood pressure in elderly and young individuals but a smaller increase in heart rate, implying that sensitiv-

ity to the vasoconstrictive effects of alpha receptor stimulation is similar in the two age groups but the sensitivity to beta receptor stimulation is different as reflected in an altered cardiac chronotropic response. It is important to note that the patients in this study received atropine as part of their premedication in order to reduce vagal stimulation. Other workers have shown that the elderly have a diminished response to anticholinergic agents (20), although detailed pharmacokinetic-pharmacodynamic responses remain to be defined.

To investigate whether the alterations in cardiac sensitivity observed in this study were reflected in changes in beta receptor function, we studied beta receptors on circulating lymphocytes obtained from the patients prior to induction of anesthesia. We have previously shown that although there is no change in B-receptor density in the elderly, the affinity of the B-receptor for adrenergic agonists decreases with advancing age (13). Physiologic changes in circulating catecholamines "down-regulate" B-receptor function in young individuals while impairment in the coupling of the B-receptor adenylate cyclase complex in the elderly accounts for the reduction in B-adrenergic responsiveness that has been shown to occur in older patients. In the present study, no age related difference was seen in either beta receptor density or the affinity of the beta receptor for the agonist isoproterenol. Thus, in this population, changes in lymphocyte beta receptors on the cell surface did not predict the sensitivity of the heart to norepinephrine stimulation during anesthesia. This may be because the alteration in beta receptor sensitivity in the elderly during anesthesia is partially due to changes in the receptor adenylate cyclase system, distal to the receptor site. For example, there is a decreased ability in the elderly to stimulate adenylate cyclase that is at least partially mediated by a deficient response of the enzyme adenylate cyclase itself (21). An additional complicating factor is that the beta receptors on lymphocytes are of the $beta_2$ subtype whereas those mediating the chronotropic effects on the heart are mainly of the $beta_1$ subtype, so that the changes seen in cardiac beta receptor sensitivity during anesthesia may not always parallel changes in lymphocyte beta receptors. It is also possible that plasma catecholamine concentrations were elevated in the preoperative period in all our subjects, due perhaps to anxiety, thereby "down-regulating" beta-receptor function so that values for beta receptor affinity (%RH) were similar in all age groups.

Differences in hemodynamic response to thiopental between the three age groups in this study might also be responsible in part for the adrenergic

and cardiovascular changes encountered in our study. A decrease in thiopental requirement has been demonstrated in elderly subjects (22); and it has been suggested that a reduced volume of distribution of the central compartment with resultant elevation in plasma thiopental concentration might lead to an increased drug effect acutely in older patients (23). However, other workers have failed to show such a change in central volume of distribution (24,25), and since no reliable dosage guidelines are available, we administered the same dose of thiopental to all our patients.

We have shown that the elderly patient has an exaggerated increase in sympathetic activity following the noxious stimulus of laryngoscopy and tracheal intubation, as manifest by increased plasma norepinephrine concentration, which is accompanied by a similar increase in blood pressure but a reduced chronotropic response, reflecting an impaired $beta_1$ receptor response but normal $alpha_1$ receptor responsiveness in these elderly patients.

References

1. Takki S, Tammisto T, Nikki P, Jaattela A: Effect of laryngoscopy and intubation on plasma catecholamine levels during intravenous induction of anaesthesia. Br J Anaesth 1972;44: 1323-8.

2. Shribman AJ, Smith G, Achola KJ: Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. Br J Anaesth 1987;59:295-9.

3. Jamill JF, Bedford RF, Weaver DC, Colohan AR: Lidocaine before endotracheal intubation: Intravenous or laryngotracheal? Anesthesiology 1981;55:578-81.

4. Tomori Z, Widdicombe JG: Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. J Physiol 1969;200:25-49.

5. Coleman AJ, Jordan C: Cardiovascular responses to anaesthesia. Anaesthesia 1980;35:972-8.

6. Safwat AM, Reitan JA, Misle GR, Hurley EJ: Use of propranolol to control rate-pressure product during cardiac anesthesia. Anesth Analg 1981;60:732-5.

7. Derbyshire DR, Smith G, Achola KJ: Effect of topical lignocaine on the sympathoadrenal responses to tracheal intubation. Br J Anaesth 1987;59:300-4.

8. Low JM, Harvey JT, Prys-Roberts C, Dagnino J: Studies of anaesthesia in relation to hypertension. VII: Adrenergic responses to laryngoscopy. Br J Anaesth 1986;58:471-7.

9. Statement on Hypertension in the Elderly. JAMA 1986;256:70-4.

10. Harris T, Cook EF, Kannel W, Schatzkin A, Goldman L: Blood pressure experience and risk of cardiovascular disease in the elderly. Hypertension 1985;7:118-24.

11. Duke PC, Wade JG, Hickey RF, Larson CP: The effects of age on baroreceptor reflex function in man. Can Anaesth Soc J 1976;23:111-24.

12. Vestal RE, Wood AJJ, Shand DG: Reduced beta-adrenoreceptor sensitivity in the elderly. Clin Pharmacol Ther 1979;26: 181-6.

13. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJJ: Alteration in leukocyte beta-receptor affinity with aging—A potential explanation for altered beta-adrenergic sensitivity in the elderly. N Engl J Med 1984;310:815-19.

14. Passon PG, Peuler JD: A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal Biochem 1973; 51:618-31.

15. Feldman RE, Limbird LE, Nadeau J, Fitzgerald GA, Robertson D, Wood AJJ: Dynamic regulation of leukocyte beta adrenergic receptor-agonist interactions by physiological changes in circulating catecholamine. J Clin Invest 1983;72:164-70.

16. Boyum A: Isolation of mononuclear cells and granulocytes from human blood. Isolation of mononuclear cells by one centrifugation, and of granulocytes by combining centrifugation and sedimentation at 1 g. Scand J Clin Lab Invest 1968; 21(Suppl. 97):77-89.

17. Munson PJ, Rodbard D: Ligand: a versatile computerized approach for characterization of ligand binding system. Anal Biochem 1980;107:220-39.

18. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265-75.

19. Wood M, Hyman S, Wood AJJ: A clinical study of sensitivity to sodium nitroprusside during controlled hypotensive anesthesia in young and elderly patients. Anesth Analg 1987;66:132-6.

20. Virtanen R, Kanto J, Iisalo E, Iisalo EUM, Salo M, Sjovall S: Pharmacokinetic studies on atropine with special reference to age. Acta Anaesthesiol Scand 1982;26:297-300.

21. Atrass IB, Scarpace PJ: Catalytic unit of adenylate cyclase: Reduced activity in aged human lymphocytes. J Clin Endocr Metab 1982;55:1026-8.

22. Christensen JH, Andreasen F, Jansen JA: Thiopentone sensitivity in young and elderly women. Br J Anaesth 1983;55:33-40.

23. Homer TD, Stanski DR: The effect of increasing age on thiopental disposition and anesthetic requirement. Anesthesiology 1985;62:714-24.

24. Christensen JH, Andreasen F, Jansen JA: Pharmacokinetics and pharmacodynamics of thiopentone. Anaesthesia 1982;37: 398-404.

25. Jung D, Mayersohn M, Perrier D, Calkins J, Saunders R: Thiopental disposition as a function of age in female patients undergoing surgery. Anesthesiology 1982;56:263-8.

Intubation with Low-Dose Atracurium in Children

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VED SA, CHEN J, REED M, FLEMING N. Intubation with low-dose atracurium in children. Anesth Analg 1989;68:609–13.

The objective of this study was to compare intubating conditions and neuromuscular effects using smaller doses of atracurium (0.25 mg/kg and 0.3 mg/kg) with the recommended dose of 0.4 mg/kg for intubation in children anesthetized with halothane, N_2O and oxygen undergoing strabismus repair. All patients (10 in each group) had good or excellent intubating conditions at 80% depression of twitch height [T1 of train-of-four (TOF) stimulation]. Mean times to intubation were 2.6 ± 0.2 minutes following 0.25 mg/kg and 2.2 ± 0.2 minutes following 0.3 mg/kg.

These times were significantly longer (P < 0.05) than the mean intubation time of 1.5 ± 0.2 minutes following 0.4 mg/kg. Mean times to recovery, defined as times from injection of atracurium to return of T1 of TOF to 10%, 25%, and 95% of control measurements, were significantly shorter with the smaller doses. Atracurium at these low doses may provide an alternative to succinylcholine for intubating children during halothane anesthesia for surgical procedures lasting 20–30 min.

Key Words: ANESTHESIA, PEDIATRIC. ANESTHETICS, VOLATILE—halothane. NEUROMUSCULAR RELAXANTS, ATRACURIUM. INTUBATION, ENDOTRACHEAL.

Succinylcholine has been used for many years to produce neuromuscular paralysis. With development of newer intermediate acting nondepolarizing muscle relaxants, the role of succinylcholine for intubation in children has become more controversial (1,2).

The primary advantages of succinylcholine are a faster onset and a shorter duration of action when compared to the currently available nondepolarizing muscle relaxants. The use of succinylcholine for intubation in children is associated with several side effects including bradycardia (3), cardiac dysrhythmias (4), postoperative muscle pain (3), masseter spasm (5), and malignant hyperthermia (6). For strabismus repair in children, use of succinylcholine poses even more risks. It interferes with the forced duction test (7,8) and there is an increased incidence of myoglobinuria (9), masseter spasm (10), and onset of malignant hyperthermia in patients genetically susceptible to it (11).

Atracurium may provide an alternative to succinylcholine for intubation in children. It is associated with fewer cardiovascular side effects (12,13) and, as a non-depolarizing muscle relaxant, it is not associated with side effects seen with succinylcholine. Most importantly atracurium is not associated with masseter spasm and it does not trigger malignant hyperthermia. However, use of atracurium for intubation in children may be disadvantageous for short procedures. To decrease the onset time of atracurium for intubation to an acceptable range, a large dose must be used with a consequent increase in duration that may far exceed the requirements for simple surgical procedures (12,13).

Existing data suggest that it may be possible to achieve a reasonably rapid onset time and a shorter duration of action with smaller doses of atracurium than those usually recommended for intubation in children. The objective of this study was to examine intubating conditions and times to recovery when two smaller doses of atracurium, 0.25 mg/kg and 0.3 mg/kg (approximately one to one and a half times the ED95 dose) were used in children scheduled for strabismus repair under halothane anesthesia, and to compare these results to those associated with the more usually recommended dose of 0.4 mg/kg (approximately twice the ED95 dose).

Methods and Materials

The protocol was approved by the Institutional Review Board on Research. Parental informed consent

was obtained. Thirty children between the ages of two and ten years (ASA physical status I and II) who required general anesthesia for an ambulatory surgical procedure to correct strabismus were studied.

Standard monitoring including a precordial stethoscope, electrocardiogram, automatic blood pressure cuff, rectal temperature probe, and a pulse oximeter were placed on all patients. Anesthesia was induced using a mask, with nitrous oxide (60%), oxygen (40%), and halothane, the concentration of which was gradually increased and then maintained at 1.5%. Anesthesia was allowed to stabilize at this level for 15 min prior to administration of the muscle relaxant.

Patients were randomly assigned to one of three groups. Following the establishment of a stable anesthetic level, patients assigned to group I (N = 10) received 0.25 mg/kg of atracurium, patients in group II (N = 10) received 0.3 mg/kg of atracurium, and patients in group III (N = 10) received 0.4 mg/kg of atracurium for intubation.

Neuromuscular function was monitored by stimulating the ulnar nerve supramaximally at the wrist using surface electrodes at 10 s intervals with train-of-four (TOF) stimuli. A control measurement of the neuromuscular response was obtained following induction prior to administration of the muscle relaxant.

All patients were intubated at 80% depression of baseline T1 twitch height. Intubating conditions of the patients were noted independently by the anesthesiologist performing the intubation, and by an independent observer, both of who were blinded as to the atracurium dose given. Intubating conditions were rated as excellent (easy passage of the tube without coughing); good (cords immobile, slight diaphragmatic movement); poor (cords moving, bucking); intubation not possible (cords apposed). These corresponded to intubation scores of 3, 2, 1, and 0 respectively. The final intubation score was a score agreed upon by both the anesthesiologist performing the intubation and by the independent observer.

Following intubation, neuromuscular function was allowed to recover spontaneously. All recovery time intervals were measured from the time of injection of the muscle relaxant. The following were also recorded: intubation time (time from injection to 80% depression of T1 of TOF), onset time (time from injection to maximum depression of T1 of TOF), maximum block (maximum percent depression of T1 of TOF), and recovery times (time taken for spontaneous recovery of T1 of TOF to 10%, 25%, and 95% of control measurements).

Comparison was made between the three groups

Table 1. Patient Data Age and Weight (Mean ± SEM)

	Group I	Group II	Group III
Age (years)	4.6 ± .91	4.2 ± .70	4.9 ± .77
Weight (kg)	19.3 ± 2.3	17.2 ± 1.6	20.4 ± 2.6
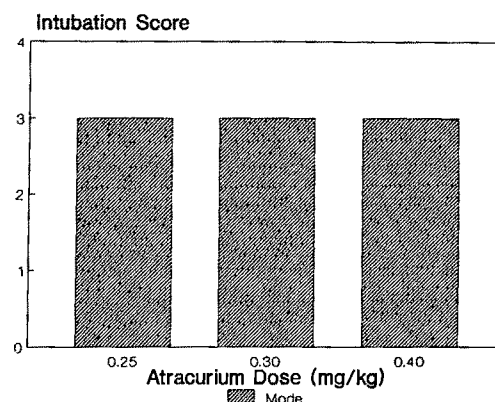
Figure 1. Intubation scores expressed as the mode (▨) for each of the three patient groups.

by analysis of variance using the Student-Newman-Keuls test. P values <0.05 were considered statistically significant. All values are reported as mean ± SEM unless otherwise noted.

Results

The three groups were comparable in age and weight (Table 1). All patients had good or excellent intubating conditions. The modes of intubation scores for each group were identical (Fig. 1).

Mean times to intubation were 2.6 ± 0.2 minutes, 2.2 ± 0.2 minutes, and 1.5 ± 0.2 minutes for groups I, II, and III respectively. Mean onset times were 4.5 ± 0.3 minutes, 3.8 ± 0.3 minutes, and 2.4 ± 0.3 minutes for groups I, II, and III respectively. Both intubation times and onset times were significantly shorter in group III than in groups I and II. There were no statistically significant differences in these variables between groups I and II (Fig. 2). All patients in group III developed 100% depression of T1. This was significantly different when compared to groups I and II, where the maximum block developed was 97% ± 0.7 and 98% ± 1.0 respectively.

The mean recovery times to T10, T25, and T95 were significantly longer in group III than in groups I and II. There were no statistical differences in these variables between groups I and II (Table 2).
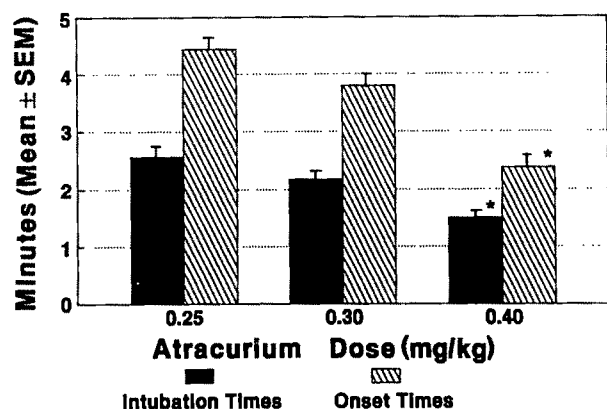
Figure 2. Summary of intubation times (80% block T_1-TOF) (■) and onset of maximal block (▧) for each of the three patient groups. *indicates $P < 0.05$ in comparison with other doses.

Table 2. Recovery Times Minutes (Mean ± SEM)

	Twitch Height (% of control)		
	T10	T25	T95
Group I	18.0 ± 1.7	23.5 ± 1.6	42.1 ± 2.6
Group II	20.3 ± 1.0	25.7 ± 1.1	45.2 ± 2.0
Group III	27.6 ± 2.0*	32.5 ± 2.2*	52.2 ± 1.7*

Summary of recovery times (10%, 25% and 95% recovery of T_1-TOF) for each of the three patient groups. *indicates $P < 0.05$ in comparison with other doses.

Discussion

The use of succinylcholine for intubation in children may be associated with various side effects. In addition to its cardiovascular effects, there is a 46% incidence of postoperative muscle pain (3) and up to a 1% incidence of masseter spasm when succinylcholine is used after halothane induction (5).

In patients with strabismus, however, there is a further increase in the incidence of side effects. Succinylcholine makes interpretation of the forced duction test unreliable for 15–20 min (7,8). There is a fourfold increase in the incidence of myoglobinuria in strabismus patients, compared to general surgical patients (9). The incidence of masseter spasm is 2.8% when halothane-succinylcholine is used in children with strabismus, fourfold greater than in children without strabismus (10). Muscle contracture tests, based on calcium uptake rates, have been said to identify malignant hyperthermia susceptibility in more than half of the children who develop masseter spasm, though the incidence of clinical malignant hyperthermia is much lower (1 in 15,000) (5). This test, however, does not permit distinction between normal and malignant hyperthermia susceptible muscle, nor does it correlate with the caffeine contracture test (14). In spite of controversy regarding the association between masseter spasm and suscep-

tibility to malignant hyperthermia (15–17), strabismus is recognized as representing an underlying myopathic disorder that may also be related to malignant hyperthermia (11).

The advantage of succinylcholine in this clinical setting is a rapid onset time and a short duration of action compared to nondepolarizing muscle relaxants. It is commonly stated that this advantage of succinylcholine far outweighs the risks and side effects associated with its use (1,2).

Atracurium has a number of theoretical advantages over succinylcholine and may provide a safe alternative for intubation in children for short surgical procedures (12,13), especially in patients that may have an increased incidence of succinylcholine associated side effects. As a nondepolarizing muscle relaxant, atracurium is not associated with any of the above side effects of succinylcholine. It is not associated with masseter spasm and does not trigger malignant hyperthermia. However, the disadvantage of using atracurium at currently recommended doses for intubation is that recovery times are longer. It was hoped that following induction of anesthesia with halothane, it would be possible to use lower doses of atracurium to produce good intubating conditions with a reasonable onset time without producing a prolonged duration of action. This study was designed to evaluate the response of two smaller doses of atracurium compared to the dose currently suggested for endotracheal intubation.

Several factors can affect intubating conditions. These include premedication, depth, duration and type of general anesthesia, intubating skills of the anesthesiologist, anatomy of the airway, and the degree of hyperventilation (12,18). Intubation of a child is often carried out under deep halothane anesthesia without any muscle relaxant. This practice may be hazardous for some children and carries the risk of hemodynamic changes associated with deep anesthesia, mechanical injury to the airway, laryngospasm, incorrect endotracheal tube placement (either in the esophagus or mainstem bronchus), coughing, and bucking after tube placement with subsequent arterial desaturation. Since the introduction of routine use of pulse oximetry in pediatric patients at our institution, it is our impression that arterial desaturation occurs more frequently when intubation is carried out under deep halothane anesthesia alone, than when intubation is facilitated by a muscle relaxant.

Satisfactory intubating conditions are usually present when neuromuscular monitoring demonstrates greater than 75–80% depressions of twitch height (18). All our patients had good or excellent

intubating conditions at 80% depression of T1 of TOF.

These results demonstrate that atracurium in doses of 0.25 and 0.3 mg/kg provide a reasonably rapid onset of action. Although intubation times were shorter following the larger dose of atracurium based on statistical analysis, the clinical significance of this difference (0.7–1.1 minutes) is minimal.

Recovery times following neuromuscular blockade is influenced by several factors. The anesthetic technique used, definitions of the recovery times, the neuromuscular monitoring technique used, age of the patient and many other pharmacokinetic and pharmacodynamic factors all of which may prolong recovery of any nondepolarizing muscle relaxant. T10, T25, and T95 recovery times were analyzed in this study to represent reversibility from neuromuscular blockade, clinical duration and complete recovery of the neuromuscular blockade respectively.

Recovery times in this study following smaller doses were significantly shorter, both clinically and statistically, when compared to the recovery times following the recommended dose of 0.4 mg/kg.

Recovery time to T10 (i.e., time to safe reversal) was over 70% shorter with the decreased dose, a factor which may significantly decrease operating room time during short procedures.

The present results must be compared with previous reports of Goudsouzian et al. (12) and with those of Brandon et al. (13), who also examined intubation times and recovery rates associated with use of atracurium in children. Goudsouzian et al. (12) studied 0.4 mg/kg atracurium in children two to ten years of age in whom anesthesia was induced and maintained with N_2O/O_2 and 1.5% inspired halothane. Neuromuscular responses were monitored with a force transducer. The mean onset time was 2.0 ± 0.3 minutes. They defined T25 and T95 recovery times from the onset of maximal neuromuscular blockade to return of twitch height to 25% and 95% of control. In their study, mean T25 recovery time was 37.6 ± 1.1 minutes and mean T95 recovery time was 68.5 ± 0.4 minutes respectively.

Brandon et al. (13), using evoked compound electromyograms, studied responses following 0.4 mg/kg atracurium in children two to ten years old in whom anesthesia was induced and maintained with N_2O/O_2 and halothane at end-tidal concentration of 0.8%. Mean onset time in their study was 2.4 ± 0.2 minutes. They did not define the recovery times but the mean T25 recovery time was 23.1 ± 1.0 minutes and mean T95 recovery time 40.0 ± 4.4 minutes. Our results are consistent with those reported by Goudsouzian et al. (12). The shorter recovery times reported by Brandon et al. may reflect less potentiation by the inhalation agent, since they used a lower concentration of halothane to maintain anesthesia.

In conclusion, use of lower doses of atracurium (approximately 50–60% of generally recommended doses) for intubation allows one to avoid the potential side effects associated with succinylcholine yet still provide good but rapidly reversible intubating conditions. Low-dose atracurium, in combination with halothane, provides a useful alternative to succinylcholine especially in patient populations where risks associated with succinylcholine may be increased and duration of the surgical procedure is short.

As a result of this study, our current practice is to use 0.25–0.3 mg/kg of atracurium for intubation of children having halothane anesthesia for short surgical procedures of 20–30 min in duration.

References

1. Delphin E, Jackson D, Rothstien P. Use of succinylcholine during elective pediatric anesthesia should be reevaluated. Anesth Analg 1987;66:1190–2.

2. Rosenberg H. Trismus is not trivial (editorial). Anesthesiology 1987;67:453–5.

3. Cook DR, Fischer CG. Characteristics of succinylcholine in infants and children. Anesthesiology 1975;42:662–5.

4. Craythorne NW, Turndorf H, Dripps RD. Changes in pulse rate and rhythm associated with the use of succinylcholine in anesthetized children. Anesthesiology 1960;21:465–70.

5. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. Anesthesiology 1984; 62:772–5.

6. Marshall BE. Malignant hyperthermia. Anesthesiology 1980; 53:395.

7. Smith RB. Succinylcholine and the forced duction test. Ophthalmol Surg 1974;5:53–5.

8. France NK, France TD, Woodburn JD, et al. Alteration in forced duction testing by succinylcholine. Anesthesiology 1979;51:S326.

9. Tammisto T, Brander P, Airaksinen MM. Strabismus as a possible sign of latent muscular disease predisposing to succinylcholine induced muscle injury. Ann Clin Res 1970;2:126–30.

10. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. Anesthesiology 1987;67:559–61.

11. Lewandowski KB. Strabismus as a possible sign of subclinical muscular dystrophy predisposing to rhabdomyolysis and myoglobinuria: a study of an affected family. Can Anaesth Soc J 1982;29:372–6.

12. Goudsouzian N, Liu LM, Cote CJ, Gionfriddo M, Rudd GD. Safety and efficacy of atracurium in adolescents and children anesthetized with halothane. Anesthesiology 1983;59:459–62.

13. Brandon BW, Rudd GD, Cook DR. Clinical pharmacology of atracurium in pediatric patients. Br J Anesth 1983;55(Suppl 1): 117S.

14. Nagarajan K, Fishbein WN, Muldoon SM, Pezeshkpour G. Calcium uptake in frozen muscle biopsy sections compared with other predictions of malignant hyperthermia susceptibility. Anesthesiology 1987;66:680-5.

15. Flewellen EH, Nelson TE. Masseter spasm induced by succinylcholine in children: Contracture testing for malignant

hyperthermia: Report of six cases. Can Anaesth Soc J 1982;29: 42-9.

16. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986;65:161-4.

17. Ellis FR, Halsall PJ. Suxamethonium spasm. A differential diagnosis concondrum. Br J Anaesth 1984;56:381-4.

18. Gergis SD, Sokoll MM, Kemmotsu O, Rudd GD. Intubation conditions after atracurium and suxamethonium. Br J Anaesth 1983;55(Suppl 1):117S.

Fifty-Five Years Ago In

Anesthesia & Analgesia

Fifty-five years ago in Anesthesia and Analgesia, 13: 75–79, 1934.
K. W. Thompson: Fatalities from Spinal Anesthesia

The author of this paper was Harvey Cushing Fellow in Surgery at the Peter Bent Brigham Hospital in Boston. That Thompson, a surgeon, understood a study like this is a reflection of the interest of his chief, Cushing, in anesthesia. Cushing was indeed a friend of anesthesia. It was he who introduced the radical idea of taking the blood pressure during anesthesia. It was he who later introduced the additional radical idea that blood pressure (and pulse) be not only taken, but recorded during anesthesia. He was codeveloper of the first formal anesthesia record. He also put together one of the most complete and most widely admired collections of printed materials on the history of anesthesia (presently housed at another institution). Thompson's contribution in this paper was twofold. First, he attempted to determine the death rate associated with spinal anesthesia. To this end he surveyed the outcomes of the 1676 patients with spinal anesthetics administered at the Brigham since it opened some 20 years earlier (i.e., about 80 spinals per year). He found that of the 77 in-hospital deaths that occurred after spinal anesthesia, eight were related to the anesthesia to a greater or lesser degree, one of which was unquestionably the result of the anesthesia. No attempt was made to determine death rate associated with other types of anesthesia. Whether spinal was safer or more dangerous cannot, therefore, be determined. Second, Thompson, after summarizing each of the eight deaths, analyzed (rather retrospectively, of course) the causes of the eight deaths associated with or due to spinal anesthesia to determine how such fatalities could be avoided. He found that decreases in blood pressure were associated with parallel decreases in heart rate. When profound (systolic pressure below 80 mm Hg; heart rate below 65), these decreases were frequent harbingers of cardiac arrest. Cardiac arrest occurred before respiratory arrest (i.e., phrenic nerves were functionally still intact, but cerebral blood flow was inadequate, leading to medullary ischemic respiratory arrest). The best preventive measures were the head-down position and ephedrine, both of which, along with the intravenous infusion of a highly diluted concentration of epinephrine, also constituted the best treatment. Thompson's conclusions about prevention and treatment of hypotension made as good physiologic sense in 1934 as they do today and can still be heard to echo, through the mouths of others, through the operating rooms of today.

Cognitive Impairment after Neuroleptanalgesia in Cataract Surgery

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CHUNG F, LAVELLE PA, McDONALD S, CHUNG A, McDONALD NJ. Cognitive impairment after neuroleptanalgesia in cataract surgery. Anesth Analg 1989;68:614–8.

This study was undertaken to evaluate the mental recovery of patients following cataract operations under neuroleptanalgesia. Mental function was assessed by Mini-Mental State (MMS) preoperatively and at 6 and 24 hours postoperatively. Preoperatively, 18.7% of the elderly had cognitive impairment of mental function while none in the younger group had any impairment (P < 0.02). At six hours postoperatively, 29.7% of the elderly had cognitive impairment compared with 4% of the younger group (P <

0.01). At 24 hours postoperatively, the percentage of elderly and younger patients with cognitive impairment had returned to preoperative levels. Baseline score and age were found to be significant predictors (P < 0.004) of the 6-hour score and 24-hour score. In conclusion, cognitive impairment of mental function occurred in patients undergoing cataract operation with retrobulbar block and intravenous sedation at 6 hours postoperatively; MMS has the potential for use as a screening preoperative test for outpatients to identify those at risk for developing cognitive impairment.

Key Words: SURGERY, OPHTHALMOLOGIC. ANESTHETIC TECHNIQUES, NEUROLEPTIC. PSYCHOLOGIC RESPONSES, CATARACT SURGERY.

The increasing prevalence of geriatric patients in our population has made the operation for senile cataract more common. Karhunen found 50 of 1505 (3.3%) patients undergoing cataract extraction developed postoperative psychiatric reactions (1). Old age and markedly deteriorated vision seemed to contribute to this complication. An impairment of memory function was shown at one week postoperatively in patients having either general or local anesthesia for cataract operations (2). No testing was done during the first six days and only memory function was tested. A significant impairment in mental function was reported in patients undergoing cataract extraction with general anesthesia on the first postoperative day (3). In that study, 48 patients received general anesthesia, and 2 received local anesthesia. Thus, the effect of mental impairment after local anesthesia and sedation was not evaluated.

A number of studies have been done to assess the effects of intravenous sedation on psychomotor re-

covery. However, these are mostly done on volunteers or healthy patients with larger doses of sedation (4,5). Patients undergoing cataract operations are usually elderly. An increasing bed shortage has made it popular to do cataract operations on an outpatient basis under retrobulbar block with intravenous sedation. No prospective study has been done to determine the mental function of these patients in the perioperative period after neuroleptanalgesia. This study was undertaken to evaluate the cognitive recovery of these patients.

Methods

The study was approved by the University Ethical Committee, and informed consent was obtained from patients. One hundred and sixteen ASA physical status I to III patients scheduled to undergo cataract operation under local anesthesia with sedation were studied. Patients with a history of psychiatric disease and those receiving psychoactive medications were excluded.

Mental function was assessed preoperatively, as well as 6 hours and 24 hours postoperatively by two investigators not involved in the anesthetic care of the patients. They were trained to administer the

Mini-Mental State test (MMS), as shown in the appendix.

The MMS is a general purpose cognitive screening test consisting of 11 items and requiring 5 to 10 min to administer. Functions tested include orientation to time and place, registration, attention and calculation, short-term recall, language ability, and the ability to copy a geometric design. The score is a weighted sum of the items. The maximum score is 30 points; a score of 23 points or below is considered evidence of cognitive impairment.

MMS is a valuable and reliable screening test of cognitive function, separating patients with cognitive disturbance from those without such change (6). It concentrates on the cognitive aspect of mental function, and excludes questions concerning mood, abnormal mental experience, and the form of thinking.

MMS scores correlated well with findings from the performance intelligence quotient (IQ) of the Wechsler Adult Intelligence Scale (7) and computerized tomography of the brain (8). Inter-rater and test-retest reliability were high, 0.83 to 0.99, in these studies. Anthonyl et al. found MMS to have a sensitivity of 87% and specificity of 82% in their evaluation of 97 consecutive medical admissions (9).

No premedication was given to our patients. The cataract operation was performed under local anesthesia with retrobulbar block supplemented by intravenous sedation. Oxygen was given by nasal prongs or mask. Increments of fentanyl, diazepam, and droperidol were given intravenously by the anesthetist in amounts necessary to produce a calm, relaxed patient, who was comfortable but cooperative, a condition mandatory for the delicate surgery involved. Intramuscular or intravenous anticholinergic medication such as atropine or hyosine was not given perioperatively. Retrobulbar block was carried out with a mixture of 2% lidocaine and 0.5% bupivacaine.

The data were divided into two groups by age: 60 years of age or older, and younger than 60. Comparison within groups between the preoperative, the 6-hour, and 24-hour postoperative MMS scores was done using Student's t-test. Comparison of the preoperative scores between the older and the younger groups was made by analysis of variance (ANOVA), and the comparison of postoperative scores in the two groups by analysis of covariance (ANCOVA). A step-wise regression was performed to determine the effect of age, preoperative score, and intravenous sedation on the change in postoperative score. $P <$ 0.05 was considered statistically significant. Data are presented as mean $(\bar{x})$ ± SE.

Table 1. Demographic Data

Age group	≥60	<60
	(N = 91)	(N = 25)
Gender	37 M:54 F	10 M:15 F
Age (yrs)	74.6 ± 7.9*	47.5 ± 10.7
	(60–87)	(24–60)
Weight (kg)	69.9 ± 1.8	66.1 ± 3.9
ASA class	I II III	I II III
	41 29 21	18 4 3
Lives alone	37%	20%

Values are mean ± SE.
*Statistically significantly different, t-test.
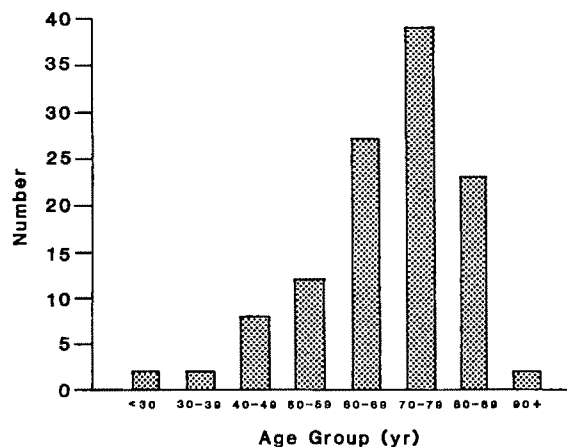
Figure 1. Age distribution.

Table 2. Mini-Mental State (MMS) Score

Age group	≥60	<60
Preop MMS	26.0 ± 0.5*	29.2 ± 0.2
6-hrs MMS	23.7 ± 0.5+**	28.2 ± 0.4
24-hrs MMS	26.4 ± 0.5*	29.0 ± 0.3

Values are mean ± SE.
*Between group ANOVA
**Within group t-test ⎤ —statistically significant
+Between group ANCOVA ⎦

Results

The demographic data are shown in Table 1 and Fig. 1. Ninety-one of the 116 patients were 60 years of age or older, and 25 were younger than 60. The mean ages of the older and younger groups were the only statistically significant differences between the two age groups.

Mean preoperative MMS scores were significantly lower in the older group than in the younger group (26.0 ± 0.5 vs 29.2 ± 0.2, Table 2). At six hours postoperatively, there was a significant decrease in MMS scores in both the older and the younger group (Table 2). The decrease in MMS score at six hours postoperatively was significantly greater in the older
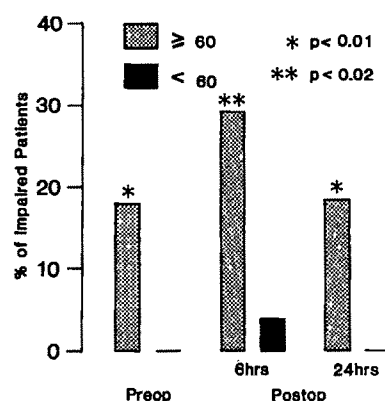
Figure 2. Percentages of younger (under 60 yrs) and elderly (60 yrs and over) patients with cognitive impairment preoperatively and 6 and 24 hours postoperatively.

group. At 24 hours postoperatively, MMS scores in both groups had returned to their preoperative levels.

Using a preoperative MMS score of 23 or less as indicative of cognitive impairment, one patient out of 25 in the younger group became impaired at 6 hours. Of the 91 elderly patients, 15 were impaired preoperatively and at 6 hours, 12 were not impaired preoperatively but were impaired at 6 hours, 62 were not impaired either preoperatively or postoperatively, and 2 were impaired preoperatively but not at 6 hours. Preoperatively 18.7% of the older group had cognitive impairment while none in the younger group had any impairment ($P < 0.02$, Fig. 2). At six hours postoperatively, significantly more (29.7%) of the elderly group had cognitive impairment compared with 4% of the younger group out of 25 patients (Fig. 2). At 24 hours postoperatively, the percentage of patients with cognitive impairment had returned to preoperative level in both groups (18.7% vs 0%, Fig. 2).

Most patients received intravenous fentanyl (25–125 μg) and diazepam (0.5–10 mg). One-third of the patients received droperidol (0.5–2.5 mg). There was no statistical difference in the amount of fentanyl, diazepam, droperidol, and 24-hour postoperative codeine given between the older and the younger group (Table 3).

Pearson's correlation coefficient revealed no association between changes in MMS scores at 6 and 24 hours postoperatively with fentanyl, diazepam, droperidol, or codeine. Furthermore, when all the drugs were considered simultaneously using a step-wise regression analysis, no association was found between the amount of intravenous drugs and changes in MMS score at 6 hours and 24 hours postoperatively.

Table 3. Intraoperative and Postoperative Drugs

Age group	≥60	<60
Fentanyl (μg)	62.1 ± 3.5	56.6 ± 4.9
	(N = 82)	(N = 25)
Diazepam (mg)	3.2 ± 0.7	3.7 ± 0.4
	(N = 71)	(N = 24)
Droperidol (mg)	1.2 ± 0.1	1.1 ± 0.2
	(N = 32)	(N = 11)
Postoperative codeine (mg per 24 hr)	83.5 ± 11.3	63.3 ± 10.5
	(N = 23)	(N = 9)

Values are mean ± SE.
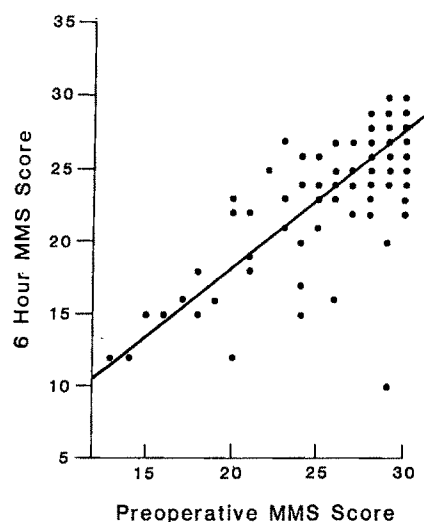
Figure 3. Correlation coefficient between 6-hr MMS score and preoperative score was significant (0.7).

Regression analysis indicated that the older patients were significantly more likely to demonstrate a lower 6-hour and 24-hour score. A binary variable indicating whether the patient had a score above or below 23 preoperatively was used to determine if low baseline scores were associated with lower 6-hour and 24-hour scores. Baseline scores were found to be significant predictors of the six-hour (Fig. 3) and 24-hour scores. The correlation coefficients of the 6-hour score and the preoperative score (0.7), and for the 24-hour and preoperative score (0.68) were statistically significant. However, the binary variable was the more important of the two significant predictors as it accounted for approximately 50% of the variance explained by the regression analysis whereas age accounted for about an additional 3%.

Discussion

As shown in Table 3, the amount of intravenous sedation used in this study was of low-dosage range. We found a decrease in cognitive function in both the

younger and the older age groups at six hours post-operatively but this had returned to baseline at 24 hours postoperatively. The elderly group had lower preoperative MMS scores and a larger decrement than the younger group following sedation. Preoperatively, one-fifth of the elderly had cognitive impairment, compared with one-third at six hours postoperatively.

Although in this study no objective measurement of differences in outcome with different postoperative MMS scores was made, the finding that perioperative cognitive impairment exists at six hours postoperatively in patients given neuroleptanalgesia is pertinent and important. Some patients may have difficulty remembering postoperative instructions if given at this time. Advice regarding care of the operative eye, medication, and follow-up appointment should be given to the patient before the operation, preferably in conjunction with written instructions for subsequent reference.

In the elderly outpatient, quality of home care is important because 37% of our patients lived alone. For the others not living alone, the responsible person may be someone even older than the patient. With the decrease in cognitive function, we need to ensure that these outpatients are accompanied home with a responsible person. In some cases, home-care services may have to be mobilized to ensure proper postoperative care. This is especially important for elderly patients and for those with a low preoperative score.

Reasons for postoperative confusion in the elderly are many and varied. Approximately one-third of patients admitted to geriatric departments have confusional states within the first month of admission (10). The incidence of delirium after cataract surgery varies from 0.3% to 15.9% (11-13). In the past, delirium after cataract surgery was attributed to sensory deprivation from bilateral eye patching (14). Only unilateral patching of the operated eye is done now. There is evidence of an association between preoperative chronic organic brain syndrome and postcataractectomy delirium (15). Anticholinergic eye drops, which are always used in combination with cataract surgery, may contribute to the development of psychiatric reactions. Mydriatic agents have been shown to induce delirium at therapeutic doses (16). Tricyclic and related antidepressants may also interact with anesthetic agents to cause postoperative confusion (17).

It was surprising that we found no specific association between changes in MMS scores at 6 and 24 hours postoperatively with the amount of intravenous sedation and the type of intravenous sedation used, but MMS scores did decrease at six hours

postoperatively showing the effect of intravenous sedation.

We did not study a comparable group of patients not having surgery and sedation, and thus failed to show the temporal variability of the test. Nevertheless, the important point was that 15 patients who were impaired preoperatively remained impaired postoperatively and 12 patients who were not impaired preoperatively became so, at least temporarily, postoperatively. Age and baseline preoperative MMS scores were significant predictors of the 6-hour and 24-hour scores. The patients who were older and had preoperative MMS scores less than 23 were more likely to demonstrate a lower score at 6 and 24 hours postoperatively. Thus MMS may have the potential for use as a screening preoperative test in geriatric patients to identify those at risk for developing cognitive impairment.

Two patients who were impaired preoperatively became less so postoperatively at 6 hours. This may be explained by a possible learning effect of repeating the tests.

In summary, we have demonstrated that cognitive impairment of mental function could occur in patients undergoing cataract surgery with retrobulbar block and intravenous sedation at 6 hours postoperatively. This lowered cognitive mental function returned to baseline at 24 hours postoperatively. Patients with a low preoperative MMS score were more likely to experience greater postoperative mental impairment than were patients with higher MMS scores preoperatively. MMS has the potential for use as a screening preoperative test for outpatients to identify those at risk for developing cognitive impairment.

APPENDIX—"MINI-MENTAL STATE"

Maximum Score	Score	
		ORIENTATION
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we: (state) (county) (town) (hospital) (floor)?
		REGISTRATION
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he learns all 3. Count trials and record.

Trials _____

ATTENTION AND CALCULATION

5   ( ) Serial 7's. 1 point for each correct. Stop after 5
          answers.
          Alternatively spell "world" backwards.

RECALL

3   ( ) Ask for the 3 objects repeated above. Give 1 point
          for each correct.

LANGUAGE

9   ( ) Name a pencil, and watch (2 points)
          Repeat the following "No ifs, ands or buts." (1
          point)
          Follow a 3-stage command:
          "Take a paper in your right hand, fold it in half,
          and put it on the floor"
          (3 points)
          Read and obey the following:
          CLOSE YOUR EYES (1 point)
          Write a sentence (1 point)
          Copy design (1 point)

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30   Total score

References

1. Karhunen U, Orko R. Psychiatric reactions complicating cata-ract surgery: a prospective study. Ophth Surg 1982;13:1008–12.

2. Karhunen U, Jonn G. A comparison of memory function following local and general anaesthesia for extraction of senile cataract. Acta Anaesthesiol Scand 1982;26:291–6.

3. Burrows J, Briggs RS, Elkington AR. Cataract extraction and confusion in elderly patients. J Clin Exp Gerontology 1985;7: 51–70.

4. Korttila K. Postanesthetic cognitive and psychomotor impair-ment. Int Anesthesiol Clin 1986;24:59–74.

5. Korttila K. Clinical effectiveness and untoward effects of new agents and techniques used in intravenous sedation. J Dent Res 1984;63:848–52.

6. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

7. Folstein MF, McHugh PR. Psychopathology of dementia: im-plications for neuropathology. In: Katzman L, ed. Congenital and Acquired Cognitive Disorders. New York: Raven Press, 1979, 17–30.

8. Tsai L, Tsang MT. The Mini-Mental State test and computer-ized tomography. Am J Psychiatry 1979;136:436–9.

9. Anthony JC, LeResche L, Niaz V, Von Korff MR, Folstein MF. Limits of the "Mini-Mental State" as a screening test for dementia and delirium among hospital patients. Psychol Med 1982;12:397–408.

10. Hodkinson HM. Mental impairment in the elderly. J Roy Coll Physicians Lond 1973;7:305–17.

11. Ziskind E, Jones H, Filante W, et al. Observations on mental symptoms in eye patched patients: hypnagogic symptoms in sensory deprivation. Am J Psychiatry 1960;116:893–900.

12. Jackson CW. Clinical sensory deprivation: A review of hospi-talized eye-surgery patients. In: Zubek JP, ed. Sensory Depri-vation: 15 Years of Research, 1st ed. New York: Appleton-Century-Crafts, 1969.

13. Summers WK, Reich TC. Delirium after cataract surgery: review and two cases. Am J Psychiatry 1979;136:4A:386–91.

14. Ziskind E, Augsburg T. Hallucinations in sensory deprivation method or madness. Science 1962;137:992–3.

15. Linn LE, Kahn RL, Coles R, et al. Patterns of behavior disturbance following cataract extraction. Am J Psychiatry 1954;100:281–9.

16. Carpenter WT. Precipitous mental deterioration following cy-cloplegia with 0.2% cyclopentolate HCl. Arch Ophthalmol 1967;78:445–7.

17. Chung F, Meier R, Lautenschlaeger E, Carmichael FJ, Chung A. General or spinal anesthesia: which is better in the elderly? Anesthesiology 1987;67:422–7.

Dose-Related Prolongation of Hyperbaric Tetracaine Spinal Anesthesia by Clonidine in Humans

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BONNET F, BRUN-BUISSON V, SAADA M, BOICO O, ROSTAING S, TOUBOUL C. Dose-related prolongation of hyperbaric tetracaine spinal anesthesia by clonidine in humans. Anesth Analg 1989;68:619–22. ·

The effect of clonidine, an α2 agonist, on sensory and motor blockade during spinal anesthesia was studied in 44 ASA physical status I II patients scheduled for orthopedic surgery. The patients were randomly allocated into three groups given 15 mg of 0.5% hyperbaric tetracaine (HT), within group I (N = 14) 1 ml isotonic saline, in group II (N = 15) 0.5 ml saline solution and 0.5 ml clonidine (75 μg), and in group III (N = 15) 1 ml clonidine (150 μg). Sensory blockade (SB) was evaluated by pinprick and motor blockade (MB) according to Bromage's scale. The level of SB was comparable in the three groups but the duration was different. The 75 μg clonidine was associated with 25% prolongation of SB at L2 and 29% prolongation of grade 3 MB Clonidine 150 μg prolonged the time of SB at L2 by 72% and grade 3 MB by 96%. Colloid infusion and the decrease in diastolic blood pressure were significantly greater in the clonidine 150 μg group compared to group I. A dose related prolongation of spinal anesthesia is demonstrated with clonidine.

Key Words: ANESTHETIC TECHNIQUES, spinal. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY: clonidine.

Alpha adrenoreceptor agonists prolong the duration of sensory blockade (SB) induced by spinal tetracaine (1). This effect is obtained with clonidine, an alpha 2 adrenergic agonist, when it is administered spinally with hyperbaric tetracaine (HT) in laboratory animals (2,3).

A recent report has documented clonidine as a useful adjunct to isobaric bupivacaine spinal anesthesia in humans (4). The dose-response relationship of intrathecal clonidine has, however, not been determined in patients having spinal anesthesia. Also, although previous studies in animals (2,3) and patients (4) showed very few hemodynamic effects when clonidine was added to local anesthetics for spinal anesthesia, clonidine has hypotensive effects in humans (5) and a legitimate concern is whether spinally injected clonidine might cause hypotension in patients. The aim of this study, therefore, was to evaluate in humans whether a dose-effect relation-ship exists when clonidine is administered with HT and if hemodynamic side effects are possibly related to clonidine spinal injection.

Material and Methods

Forty-four patients scheduled for orthopedic surgery were studied after informed consent and ethics committee approval. Patients were allocated randomly to three groups. In group I (HT group), 14 patients received 3 ml 0.5% tetracaine in a 10% (HT) dextrose plus 1 ml isotonic saline solution; in group II (HT C-75 group) 15 patients received 3 ml HT plus 0.5 ml isotonic saline solution and 75 μg clonidine (0.5 ml), in group III (HT C-150 group) 15 patients received 3 ml HT plus 150 μg clonidine (1 ml). In all three groups, premedication consisted of 1 mg of oral flunitrazepam. Spinal anesthesia was performed in sitting position with a 22 gauge needle at the L 2-3 or L 3-4 space. Patients were immediately placed in the supine position. A colloid solution (Plasmion) was infused intravenously over the first 30 minutes (10 ml/kg) following the spinal injection. The level of SB was evaluated by pin-prick. Motor blockade (MB) was evaluated using the Bromage's scale (6): 0 = no

Table 1. Clinical Features of the Patients

	Group I (HT)	Group II (HT C-75)	Group III (HT C-150)
Sex (M/W)	9/5	7/8	6/9
Age (years)	45.6 ± 15.2	40.8 ± 21.9	49.6 ± 18.2
Weight (kg)	60.2 ± 13.5	65.8 ± 16.2	56.9 ± 8.3
Height (cm)	165 ± 10	166 ± 12	164 ± 8

impairment of movements of legs and feet to 3 = complete motor blockade of lower limbs. Measurements of SB and MB were made very 5 minutes for 30 minutes, then every 30 minutes until recovery of sensory and motor function was complete. Blood pressure and heart rate were measured with an automatized sphygmomanometer at 2.5-minute intervals throughout anesthesia and surgery and at 10 minute intervals in the postoperative period. When blood pressure decreased more than 20% of preinduction control value, the rate of infusion of colloid was increased. If this did not restore blood pressure to a value at least 80% of the control, 3 mg of ephedrine were injected i.v.

Statistical analysis used a 2 way ANOVA, Student's t test and chi-square with the Yates correction when appropriate. Values were expressed as mean ± SD. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences among the three groups in age, weight, or height (Table 1). The level of SB was also comparable in the three groups (Table 2). The duration of SB was significantly prolonged in group III (HT C-150) (Fig. 1). Indeed clonidine 150 μg increased the time for SB regression to L2 by 72% while clonidine 75 μg prolonged SB time for regression to L2 by only 29% (Table 2). All patients except one in each clonidine group, had grade 3 MB (Fig. 2). The duration of MB was also significantly longer in group III than in groups I and II (Table 3). Duration of grade 3 MB with 150 μg was 96% longer than control group and 29% longer with 75 μg clonidine (Table 3). Changes in systolic blood pressure were similar in the three groups (Table 4), while the decrease in diastolic blood pressure, though moderate, was significantly greater in group III than in group I but not significantly different from group II. The amount of colloid infused was more important in group III (Table 4). The incidence of bradycardia was not significantly different in the three groups. A lower extremity tourniquet was used during surgery in 10 patients in each group. Five patients experienced tourniquet pain in group I but only two in the two other groups.

Discussion

This study confirms in humans a dose related prolongation of SB and MB by clonidine during HT spinal anesthesia. When the dose of clonidine was doubled from 75 to 150 μg the percentage of change from control duration of the time for SB regression to L2 was almost doubled. Duration of grade 3 MB (L5-S1) was three times greater but the percentage success rate of grade 3 MB was similar in the three groups. Bedder et al. have previously shown in an animal study that 150 μg of clonidine is more effective in increasing the duration of MB than the duration of SB (3). Mensik et al. reported a relationship between the clonidine dose and the duration of either SB or MB but a plateau was reached at a clonidine dose of 150 μg with no additional effect for a 300 μg dose (2).

The decrease in the incidence of tourniquet pain in the two groups of patients given clonidine suggests that the quality of the SB was also improved, although the groups of patients were not randomized to assess this point. The incidence of tourniquet pain observed with hyperbaric tetracaine can be appreciable (7) and the addition of clonidine could be an attractive means to resolve this problem.

Several mechanisms could account for the effect of spinal clonidine observed in this study. Intrathecal or epidural clonidine have for example analgesic properties through an opiate independent mechanism (8–10). Spinal and supra-spinal sites have been suggested for clonidine action (11,12). In addition, clonidine is a vasoconstrictor agent (13,14). Clonidine constricts central nervous system arteries in vitro (15) and epidural clonidine decreases spinal cord blood flow in pigs (16) and rats (17) although this has not been documented in sheep (18). By contrast, tetracaine has a local vasodilating effect increasing spinal cord blood flow and this effect is antagonized by α adrenergic stimulation (19). Therefore, clonidine might antagonize the vasodilating effect of tetracaine, thereby delaying vascular absorption of tetracaine. The fact that clonidine prolongs motor blockade as well as sensory blockade might be an indirect argument for a delayed absorption of tetracaine.

Our study documents that clonidine has only minor effects on blood pressure during HT spinal anesthesia. A previous study also found the absence of significant hemodynamic effects when clonidine was administered with isobaric bupivacaine (4). Since the hemodynamic consequences of the administration of hyperbaric solutions during spinal anesthesia are said to be more marked than those of isobaric solutions, when the extent of sensory blockade is greater one might be concerned that clonidine could

Table 2. Features of Sensory Spinal Blockade

	Group I (HT)	Group II (HT C-75)	Group III (HT C-150)
Maximum level of sensory blockade	15.7 ± 2.5	15.5 ± 2.3	17.4 ± 2.4
Extension (segments)	(T10–T4)	(T10–T2)	(T10–T2)
Time to achieve maximum level of sensory blockade (min)	18.2 ± 17.5	12.3 ± 7.0	26.3 ± 2.4
Time for 2 segment regression (min)	85.3 ± 34.2	105.3 ± 65.7	134.3 ± 70.1*
Time for regression of sensory blockade to L2 (min)	178 ± 68	229 ± 84	306 ± 93*

*$P < 0.05$: Intergroup comparison, significant difference from Group I
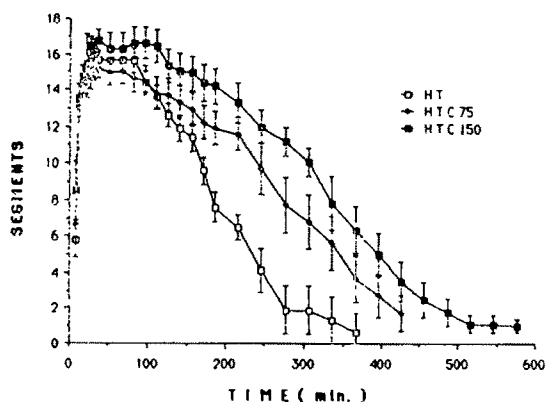
Figure 1. Number of spinal segments with sensory blockade as a function of time (in minutes) in the three groups of patients. HT, hyperbaric tetracaine (N = 14). HT C-75, hyperbaric tetracaine plus clonidine 75 μg (N = 15). HT C-150, hyperbaric tetracaine plus clonidine 150 μg (N = 15).
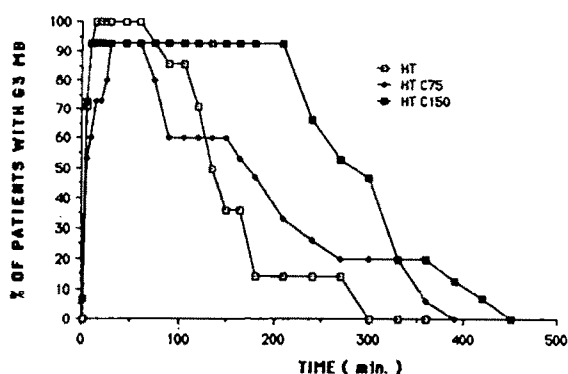
Figure 2. Grade 3 motor blockade as a function of time (in minutes). HT, hyperbaric tetracaine (N = 14). HT C-75, hyperbaric tetracaine plus clonidine 75 μg (N = 15). HT C-150, hyperbaric tetracaine plus clonidine 150 μg (N = 15).

Table 3. Features of the Motor Blockade

	Group I (HT)	Group II (HT C-75)	Group III (HT C-150)
Number of Patients with Grade 3 MB	14/14	13/15	14/15
Time to Onset of Grade 3 MB (min)	6.4 ± 2.3	10.1 ± 0.7	5.7 ± 2.7
Duration of Grade 3 MB (min)	137 ± 61	177 ± 107	268 ± 77**†
Duration of Grade 2 MB (min)	162 ± 65	191 ± 110	316 ± 75**†
Duration of Grade 1 MB (min)	198 ± 73	232 ± 109	372 ± 76**†

Grade of motor blockade (MB) using the Bromage scale (6)
**$P < 0.01$ Comparison between Group I and Group II
†$P < 0.05$ Comparison between Group II and Group III

be associated with additional lowering in blood pressure (20). Most animal studies have shown, however, that spinal clonidine does not worsen the decrease in blood pressure induced by the spinal injection of a local anesthetic, and clonidine itself had no important hemodynamic consequences when administered spinally or epidurally (2,3,4,9,16,18). Only with epidural doses of clonidine greater than 3 μg/kg is blood pressure significantly changed (16,21). A reduction of sympathetic outflow is of primary importance for the hypotensive effect of clonidine (22). Since spinal anesthesia with local anesthetics produces an extended sympathetic blockade (23), the addition of clonidine cannot further depress sympathetic activity that is already totally blocked. Indeed, a peripheral vasoconstrictive effect seems to be responsible for hypertension when clonidine is injected intrathecally or epidurally in doses so great that pharmacologically active concentrations of clonidine are achieved in peripheral blood (9,16).

Bradycardia occurred more frequently, although not significantly so, in our patients after a 150 μg clonidine dose than in the other two groups. Bradycardia associated with clonidine is thought to be related both to a reduction in sympathetic activity and to an increase in vagal tone mediated by the supraspinal action of clonidine (22). After spinal administration clonidine might reach supraspinal sites either by means of vascular absorption or by cephalad migration into the cerebrospinal fluid in the brainstem.

Clonidine appears to be an alternative to epinephrine to prolong the duration of hyperbaric tetracaine spinal anesthesia in humans, confirming data reported with spinal bupivacaine (4,24). The effect of clonidine is dose dependent.

Table 4. Heart Rate and Blood Pressure

	Group I (HT)	Group II (HT C-75)	Group III (HT C-150)
Maximum Decrease * in SAP (%)	35.1 ± 10.7	34.3 ± 15.7	34.3 ± 10.5
Maximum Decrease * in DAP (%)	31.7 ± 10.7	36.6 ± 15.2	42.7 ± 11.4**
Number of Patients* with a Decrease in HR ≤ 45/min	3/14	3/15	6/15
Number of Patients Requiring I.V. Ephedrine	3/14	2/15	5/15
Colloid infusion ml·kg^{-1}·min^{-1}	12.3 ± 4.5	16.0 ± 8.1	18.3 ± 11.3**

*Below preinduction levels
**$P < 0.05$ comparison between Group III and Group I
SAP, systolic arterial pressure; DAP, diastolic arterial pressure

References

1. Concepcion M, Maddi R, Francis D, Rocco AG, Murray E, Covino BG. Vasoconstrictors in spinal anesthesia with tetracaine: a comparison of epinephrine and phenylephrine. Anesth Analg 1984;63:134-8.

2. Mensik FJ, Kozody R, Kehler CH, Wade JG. Dose-response relationship of clonidine in tetracaine spinal anesthesia. Anesthesiology 1987;67:717-21.

3. Bedder MD, Kozody R, Palahniuk RJ, Cumming MO, Pucci WR. Clonidine prolongs canine tetracaine spinal anesthesia. Can Anesth Soc J 1986;33:591-6.

4. Racle JP, Benkhadra A, Poy JY, Ghizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 1987;66:442-6.

5. Van Zwieten PA. Antihypertensive drugs with a central action. Prog Pharmacol 1975;1:1-63.

6. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine and epidural anesthesia. Acta Anaesthesiol Scand 1965;16:55-62.

7. Bonnet F, Zozime JP, Marcandoro J, Brun-Buisson V, Touboul CH, Saada M. Tourniquet pain during spinal anesthesia: hyperbaric versus isobaric tetracaine. Regional Anesthesia 1988;13:29-33.

8. Tamsen A, Gordh T. Epidural clonidine produces analgesia. Lancet 1984;II:231-2.

9. Eisenach JC, Dewan DM, Rose JC. Epidural clonidine produces antinociception but not hypotension in sheep. Anesthesiology 1987;66:496-501.

10. Yaksh T, Reddy SVT. Studies in the primate of the analgesic effects associated with intrathecal action of opiates, alpha adrenergic agonists and baclofen. Anesthesiology 1981;54:451-7.

11. Milne B, Cervenko FW, Jhamandas K, Sutak M. Intrathecal clonidine analgesia and effect on opiate withdrawal in the rats. Anesthesiology 1985;62:34-8.

12. Post C, Gordh T, Milnor BG, Archer T, Freedman J. Antinociceptive effects and spinal cord tissue concentrations after

intrathecal injection of guanfacine or clonidine into rats. Anesth Analg 1987;66:317-24.

13. Nayler WG, Price JM, Swann JB, McInnes I, Race D, Lowe TE. Effect of the hypotensive drug St 155 (Catapres) on the heart and peripheral circulation. J Pharmacol Exp Ther 1968;164:45-59.

14. Langer SZ, Hicks PE. Alpha-adrenoreceptor subtypes in blood vessels: physiology and pharmacology. J Cardiovasc Pharmacol 1984;6:5547-58.

15. Sakakibara Y, Fujiwara M, Muramatsu I. Pharmacological characterization of the alpha adrenoreceptors of the dog basilar artery. Naunyn Schmiedebergs Arch Pharmacol 1982;319:1-7.

16. Gordh T, Feuk U, Norlen K. Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. Anesth Analg 1986;65:1312-18.

17. Crosby G, Russo M. The spinal blood flow effect of subarachnoid clonidine. Anesthesiology 1987;67:A417.

18. Eisenach JC, Grice SC. Epidural clonidine does not decrease blood pressure or spinal cord blood flow in awake sheep. Anesthesiology 1988;68:335-40.

19. Kozody R, Palahniuk RJ, Cumming MO. Spinal cord blood flow following subarachnoid tetracaine. Can Anaesth Soc J 1985;32:23-9.

20. Moller IW, Fernandes A, Edström HH. Subarachnoid anesthesia with 0.5% bupivacaine: effects of density. Br J Anaesth 1984;56:1191-4.

21. Ghignone M, Quintin L, Kozody R. Hemodynamic effects of clonidine injected epidurally in halothane anaesthetized dogs. Can Anaesth Soc J 1987;65:1312-8.

22. Kobinger W. Central blood pressure regulation: involvement of presynaptic or postsynaptic $\alpha 1$ or $\alpha 2$ adrenoreceptors? Chest 1983;83:296-9.

23. Chamberlain DP, Chamberlain BDL. Changes in the skin temperature of the trunk and their relationship to sympathetic blockade during spinal anesthesia. Anesthesiology 1986;65:139-43.

24. Racle JP, Poy JY, Benkhadra A, Jourdren L, Fockenier F. Prolonging hyperbaric bupivacaine spinal anaesthesia with adrenaline and clonidine in the elderly. Ann Fr Anesth Réanim 1988;7:139-44.

Intrathecal Somatostatin in Cat and Mouse Studies on Pain, Motor Behavior, and Histopathology

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GAUMANN DM, YAKSH TL, POST C, WILCOX GL, RODRIGUEZ M. Intrathecal somatostatin in cat and mouse: studies on pain, motor behavior, and histopathology. Anesth Analg 1989;68:623–32.

Effects of intrathecal (i.t.) somatostatin (SST) on nociception, motor function, and spinal cord pathology were evaluated in cats and mice. Cats chronically implanted with i.t. lumbar catheters received either a single injection of 2 mg SST i.t. (group I, N = 4), four repetitive injections on consecutive days of 2 mg SST i.t. (group II, N = 4) or saline i.t. (group III, N = 2). No analgesic effects were observed following single or repeated SST injections as evaluated by the skin twitch response. However, significant impairment of hind leg motor function ranging from unbalanced gait to paralysis was observed following the first SST i.t. injection. Histological examination of spinal cords six days after the first SST injection in group II showed multiple pyknotic neurons in all cats. Some cats showed focal demyelination in the posterior column of the spinal cord white matter. Mice received a single percutaneous injection of 50 µg SST i.t. (group I, N = 7), 5 µg SST i.t. (group II, N = 3), or saline i.t., (group III, N = 5). No analgesic effects were observed in groups II and III as evaluated by the hot plate (HP) and tail flick (TF) tests. Injection of 50 µg SST i.t. (group I) caused reversible flaccid hind leg paralysis in all mice and concomitant increases in HP and TF latencies. Histologic examination revealed focal demyelination in the spinal cord in three out of seven mice in this group. Present data substantiate neurotoxic effects of i.t. SST and lack of behaviorally defined antinociception at innocuous dosages.

Key Words: HORMONES, somatostatin. PAIN, experimental. SPINAL CORD, neurotoxicity.

Analgesic effects of somatostatin (SST), have been reported in humans following intrathecal (i.t.) (1) and epidural (2) administration. Though several lines of investigation suggest that SST may be acting as a transmitter (3) or modulator (4) of nociceptive information at the level of the spinal cord, its functional role is not well understood, and contradictory effects have been reported, including selective depressant actions to noxious stimuli (5), as well as general excitatory effects (6,7). Moreover, in recent experiments performed in rats, i.t. administration of SST

resulted in dose-dependent neurotoxic effects, while antinociceptive effects were only observed at (8) or slightly below (9) neurotoxic dosages. Although common pharmacological mechanisms occur in different species, evidenced by the close predictability of pharmacological effects of opioids in humans as derived from rat experiments (10), it is possible that the rat may be especially sensitive to certain endogenous peptides (11), and therefore may not be representative for the action of i.t. SST in humans. The present study was conducted to extend previous rat experiments (8) by examining antinociceptive and possible neurotoxic effects of intrathecally administered SST in the cat and the mouse.

Methods

Experiments in cats and mice were performed after approval of the respective protocols by the Mayo Foundation Animal Care Committee.

Table 1. Summary of Experimental Protocols

		Day 1	Day 2	Day 3	Day 4	Day 7
	Group I (N = 4)	SST 2 mg	†			
CATS	Group II (N = 4)	SST 2 mg	SST 2 mg	SST 2 mg	SST 2 mg	†
	Group III (N = 2)	SAL	SAL	SAL	SAL	†
	Group I (N = 7)	SST 50 µg				†
MICE	Group II (N = 3)	SST 5 µg				†
	Group III (N = 5)	SAL				†

Three groups of cats and mice were injected intrathecally with somatostatin (SST) or saline (SAL). †Marks the day animal was killed

Cat Experiments

Ten mongrel cats (3.0 ± 0.1 kg, mean ± SE) were prepared under sterile surgical conditions with chronic lumbar intrathecal (i.t.) and carotid artery catheters under halothane anesthesia. Intrathecal lumbar catheters (PE10) were placed three to five days prior to the first i.t. drug injection (12). After puncture of the atlanto-occipital membrane, catheters were advanced 30 cm caudally, to position their tips at the lumbar enlargement of the spinal cord. Correct placement of i.t. catheters was verified by dye injection on removal of spinal cords at the end of the experimental observation period. Catheters were externalized on top of the skull and plugged with a piece of steel wire. Prior to the surgical procedure, a bolus of 300,000 U of penicillin G benzathine and penicillin G procaine was administered i.m. and repeated every three days, as infection prophylaxis. Left carotid artery catheters (4 French) were implanted one day before the first i.t. drug injection for the continuous measurement of blood pressure (BP) and heart rate (1HR). Catheters were occluded with a three-way stopclock, externalized on top of the skull, and flushed with heparin (300 U).

Experimental Protocol

Cats were divided into three groups, according to the protocol of i.t. drug administration, consisting of either SST or 0.9% NaCl (Table 1). Cyclic SST-14 was a generous gift of Ferring pharmaceuticals (batch No: LM 6276). Immediately prior to the experiment, SST was prepared for i.t. injection by dilution in 0.9% NaCl. A dose of 2 mg SST in 200 µl was always administered and cleared from the i.t. catheter by

subsequent injection of 100 µl 0.9% NaCl. Control cats received a volume of 300 µl 0.9% NaCl i.t.

In group I (N = 4), a single injection of 2 mg SST was administered i.t. on day 1, and cats were killed 24 hours later. Cats in group II (N = 4) received four repetitive injections of 2 mg SST i.t. on day 1 through day 4. Cats in group III (N = 2) served as a control and received 0.9% NaCl i.t. on 4 consecutive days. Cats in groups II and III were killed six days after the first injection.

Nociception was evaluated by the skin twitch (ST) response (12). Both flanks were shaved and exposed to a temperature probe (72.5°C, tip surface area: 1 cm³) for maximally 10 sec (cutoff point). This stimulus usually produces an immediate spinally mediated local skin twitch response, followed by agitation-escape behavior. Skin twitch responses were assessed bilaterally at baseline, 5, 20, and 60 min after i.t. injection, prior to repeated i.t. injections and at the end of the experimental period.

Hind leg motor function was evaluated by observation of the cats' walking ability and rated on a scale of 0 to 3: 0 = normal; 1 = mild dysfunction, unbalanced gait; 2 = severe weakness, inability to bear weight; 3 = paralysis. Reflex motor function was further assessed on a +/− basis by the placing and stepping response. In normal cats, stepping is elicited by drawing the dorsum of either hind paw across the edge of a table, resulting in an upward lifting of the paw onto the surface of the table. When the plantar surface of the hind paw lightly touches the surface of a table, placing is evoked and the paw extends to make solid contact with the table.

Behavioral effects of i.t. drug administration were evaluated on a +/− scale. Main effects observed were excitation, piloerection, shivering, and hypersensitivity to touch. Feeding, micturition, and defecation were daily recorded. Body weight was recorded at the beginning and at the end of the experimental observation period.

In order to assess potential effects of SST on the sympathetic nervous system, BP and HR were continuously monitored (Grass model 7 polygraph) in all experimental groups during i.t. drug injection. Catecholamine plasma levels in the carotid artery were determined at baseline after the cats were allowed a 15 min adaptation period to the laboratory setting, and 30 min after i.t. drug administration, corresponding to a 10 min resting period after the previous nociceptive and behavioral test. Norepinephrine (NE), epinephrine (EPI) and dopamine (DA) levels were measured by high performance liquid chromatography as described elsewhere (13).

Mice Experiments

Male Balb/C mice (20 g, Jackson Laboratory, Bar Harbor, Maine) were subjected to a single percutaneous lumbar intrathecal injection (5 μl) (14) of either 50 μg SST (group I, N = 7), 5 μg SST (group II, N = 3), or 0.9% NaCl (group III, N = 5) as indicated in Table 1. Cyclic SST-14 (Ferring, batch No. LM 6276) was dissolved in 0.9% NaCl immediately prior to administration.

Nociception was evaluated by the hot plate (HP) and tail flick (TF) response. Hot Plate: The animal was placed in a plexiglass enclosure on a metal surface with a constant temperature of 52.5°C. The response latency was recorded as the time the animal required to lick one of its hind paws. Cutoff time in the absence of a response was 60 sec.

Tail Flick: The animal's tail was placed over a rectangular slit above an illuminated projector lamp (Sylvania 300-watt bulb). The response latency was the time required for the mouse to vigorously remove its tail off the slit. To prevent tissue damage, the cutoff time was six seconds in the absence of a response.

Motor function was assessed by observation. Hind leg flaccidity (and thus inability to walk) was assessed on a +/− scale.

Behavioral effects of i.t. SST, such as scratching, licking, and hypersensitivity to touch, were evaluated on a +/− scale.

Histology

Cats and mice were anesthetized with either halothane (cats) or pentobarbital (mice) and perfused with Trump's fixative (1.5% glutaraldehyde, 4% formaldehyde in 0.1 M phosphate buffer, pH 7.2). As indicated in Table 1, spinal cords in cats were removed 24 hours after the i.t. injection in group I, and 6 days after the first of 4 consecutive i.t. injections in groups II and III. In mice, spinal cords (groups I, II, and III) were removed six days after the single i.t. injection.

Several segments of cat spinal cords were removed from the cervical, thoracic, lumbar, and sacral cord, embedded in paraffin, and cut at 10 μm. In mice and in two cats from group II, lumbar cord segments were osmicated in 1% osmium tetroxide for 2 hours and embedded in JB-4 plastic and cut at 2 μm. Paraffin sections were stained with Luxol Fast Blue, while methacrylate plastic sections were stained with modified erichrome stain counterstained with cresyl violet to detect demyelination. Sections were evaluated by an observer (blinded for different treatment groups),

Table 2. Behavioral Effects of i.t. SST in Cats

Response	Total dose of SST i.t.			
	2 mg	4 mg	6 mg	8 mg
	Day 1 (N = 8)	Day 2 (N = 4)	Day 3 (N = 4)	Day 4 (N = 4)
Excitation/ Hypersensitivity	3/8	4/4	3/4	3/4
Shivering/ Piloerection	2/8	1/4	2/4	1/4

Behavioral response during 20 min following SST i.t. injection evaluated on a +/− basis. Numbers refer to cats showing a positive response versus total number of cats examined.

for signs of neuronal damage, inflammatory response or demyelination.

Data Analysis

Skin twitch responses in cats were assessed bilaterally prior to and 5, 20, and 60 minutes following single (group I) and repeated (groups II and III) i.t. drug injections. Response analysis was performed after averaging the skin twitch response from right and left sides and calculating the maximum percent effect (MPE) according to the following equation: MPE = (postdrug response latency − predrug response latency) × (cutoff latency − predrug response latency)$^{-1}$ × 100. The maximum values of the MPEs during 1 hr after injection and MPEs prior to repeated injections (group II) were compared to pre-injection values at day 1 (MPE = 0) by paired *t*-test.

HP and TF tests in mice were evaluated on day one at baseline prior to i.t. injection (saline, SST 5 and 50 μg) and 3, 10, and 30 min after injection. Results were analyzed by paired *t*-test after calculation of the MPEs.

Paired *t*-tests were further employed to analyze hemodynamic response and catecholamine plasma levels in cats.

Effects of SST on motor and behavioral function in cats and mice were evaluated by Chi-square tests. A *P* value of 0.05 was considered statistically significant.

Results

Cat Experiments

The behavioral effects of i.t. SST in cats are summarized in Table 2. Single and repeated injections of 2 mg SST i.t. often evoked an excitatory response with vocalization and escape behavior. Some cats immedi-
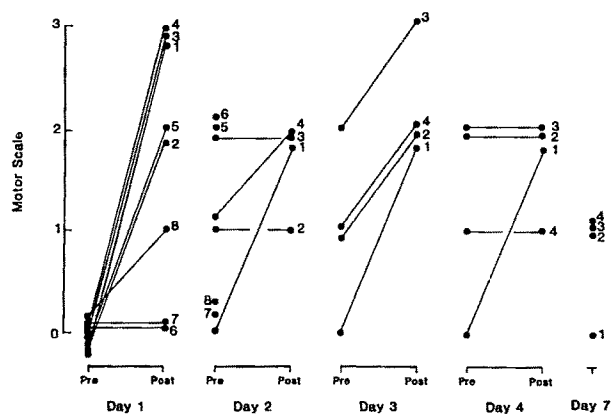
Figure 1. Effects of i.t. somatostatin (SST) on hind leg motor function in cats, graded on a motor scale of 0 to 3 (0 = normal, 1 = mild dysfunction, 2 = severe dysfunction, 3 = paralysis). Values are shown for individual cats (numbered 1 to 8) prior to (pre) and after (post) single (day 1, N = 8) or repeated (days 2, 3, 4; N = 4) i.t. injections of 2 mg SST. "Post" values represent the highest score observed during a 1 hr period following SST injection. "Pre" values on day 2 for cats no. 5, 6, 7, and 8 and on day 7 for cats no. 1, 2, 3, and 4 mark values prior to killing of the animals.

Figure 2. Effects of i.t. somatostatin (SST) on skin twitch response in cats (cutoff latency 10 sec). Values are shown for individual cats (numbered 1 to 8) prior to (pre) and after (post) single (day 1, N = 8) or repeated (days 2, 3, 4; N = 4) i.t. injections of 2 mg SST. "Post" values represent the highest latency obtained during a 1 hr period following SST injection. "Pre" values on day 2 for cats no. 5, 7, and 8 and on day 7 for cats no. 1, 2, 3, and 4 mark values prior to killing of the animals. Cat no. 6 on day 2 was not examined due to general weakness.

ately developed marked hypersensitivity to touch of their hind legs, resulting in aggressive behavior, which was most pronounced within the first 20 min after injection. Within this same time frame, some cats exhibited piloerection and shivering. Shivering sometimes extended over the whole body, whereas piloerection was limited to hindquarters and flanks. The i.t. injection of saline in two control cats evoked no behavioral responses.

Effects of i.t. SST on motor function were limited to the hind legs and developed within 5 minutes following SST i.t. injection. The degree of hind leg motor dysfunction improved or deteriorated in any given cat during the following 1-hour observation period. Figure 1 presents the worst motor scores during a 1-hour observation period following i.t. SST injection in individual cats. Thus, with the first SST 2 mg i.t. injection on day 1 (groups I and II), six out of the eight cats examined developed hind leg motor dysfunction (mild: N = 1; severe: N = 2; paralysis: N = 3). Paralysis was flaccid in two of these cats and spastic in one. Within the following 24 hrs, motor dysfunction improved in most of the cats, but only two cats regained normal function. One cat (no. 6) with no motor impairment following i.t. SST, developed signs of respiratory infection and severe general weakness overnight and thus achieved a motor score of 2 on day 2.

Repeated injection of 2 mg SST i.t. (group II) generally caused less severe effects on motor function

than the first injection did. Similar to the effects on day 1, there was a tendency to improved motor function within 24 hrs following repeated injections. No case of permanent paralysis or severe motor dysfunction was observed on day 7. After a total cumulative dose of 8 mg SST i.t., cats mainly showed mild hind leg motor dysfunction (N = 3). Motor dysfunction on a +/- scale was significant (Chi-square test) on day 1.

The placing and stepping reflexes were consistently present in normal cats (motor scale 0) and absent in cats with hind leg paralysis (motor scale 3). With mild to severe hind leg dysfunction (motor scale 1 and 2), the reflex responses were variable.

The two cats injected with i.t. saline (group III) had normal hind leg motor function throughout the observation period.

Skin twitch response latencies, indicating nociception, are presented in Figure 2 for individual cats following i.t. SST injections. With the first injection on day 1, either an increase (N = 4), no change (N = 2) or a slight decrease (N = 2) in response latencies was observed. Within the following 24 hours, response latencies tended to decrease, paralleling the trend of improved motor function values. Skin twitch responses remained variable with repeated injections. Overall no significant antinociceptive effect of SST injections was detected by analysis of MPEs, neither with regard to post injection values nor to values prior to repeated injections. Control cats (group III) showed no change in the skin twitch latencies following single and repeated i.t. saline injections as evidenced by MPE values between ±20%.

Table 3. Effects of i.t. SST on Sympathetic Response in Cats

	MABP (mm Hg)	HR (bpm)	NE (ng/ml)	EPI (ng/ml)	DA (ng/ml)
Pre i.t. SST	113 ±10	193 ±14	0.16 ±0.08	0.15 ±0.02	0.08 ±0.01
Post i.t. SST	123 ±9	189 ±14	0.22 ±0.06	0.26* ±0.04	0.07 ±0.01

Mean arterial blood pressure (MABP), heart rate (HR), and carotid artery plasma levels of norepinephrine (NE), epinephrine (EPI), and dopamine (DA) (mean ± se) in 8 cats, prior to (pre) and 30 min after (post) intrathecal (i.t.) injection of 2 mg somatostatin (SST). In 3 cats data were pooled from 2 measurements on day 1 and day 2.
(*$P < 0.05$ evaluated by paired t-test).

BP and HR were measured in all cats during i.t. drug injection on day 1, and in three cats, in which the carotid artery catheters remained patent, also on day 2. Injection of SST i.t. generally evoked an immediate increase in BP which was occasionally associated with cardiac arrhythmias. A summary of the hemodynamic and corresponding catecholamine response is shown in Table 3. The excitatory and apparently stressful event caused by i.t. SST injection is evidenced by a small, though significant, increase above pre-injection levels in epinephrine plasma levels 30 min after injection. The two control cats on day one, showed 30 min after i.t. administration of saline, the following changes from pre-injection values: MABP: +20, −10 mm Hg, HR: −10, −10 bpm, NE: −0.78, −0.26 ng/ml, EPI: −0.19, −0.08 ng/ml, DA: −0.01, +0.23 ng/ml.

Following SST injections, cats showed normal feeding behavior, and body weight remained stable throughout the observation period. Two cats (N = 1 in group I, N = 1 in group II) developed acute urinary retention during the first 24 hrs after SST injection. The cat in group II subsequently developed an overflow bladder with a rest urine volume of 50 ml as determined on day 7 by catheterization.

Histological examination of spinal cord segments showed no pathologic abnormalities in control cats (Figure 3A) treated with repetitive injections of saline and killed on day 7 (group III) as well as in cats treated with a single injection of 2 mg SST i.t. and killed on day 2 (group I). However, cats given a total dose of 8 mg SST i.t. by repetitive injections and killed on day 7 (group II) showed multiple small dark pyknotic neurons (N = 4), marked nucleolysis (N = 1), and inflammatory response (N = 2) in the grey matter of the spinal cord below the tip of the catheter (Figure 3B). Sections from two cats in this group were processed for plastic embedded sections to determine if additional abnormalities were noted in the myelin sheaths. Both cats showed focal areas of demyelina-

tion in the posterior column of the white matter, immediately adjacent to the posterior horn (Figure 3C). The myelin had gross vacuoles which appeared to arise from splitting of the myelin sheaths. Most axons in this area of vacuolar demyelination were preserved. There was a conspicuous absence of inflammatory cells, suggesting the myelin dissolution was a direct effect of SST. Most of the neurons adjacent to the area of demyelination were preserved and looked morphologically normal, while some showed signs of degeneration. Present also was a perivascular inflammatory response in meningeal blood vessels. Pathologic findings were always limited to lumbar and sacral segments and did not involve dorsal root ganglia.

Mice Experiments

Behavioral effects of i.t. SST administration in mice are presented in Table 4. Characteristic scratching and licking behavior limited to hindquarters and flanks were observed in 5 out of 7 mice given 50 μg SST i.t. This response occurred mainly within 30 to 60 sec after injection and was not observed in mice treated with saline or 5 μg SST i.t. A period of hyperexcitability to touch followed 1 to 3 minutes after injection in two mice each, which had received 5 μg or 50 μg SST. This hyperexcitability was not limited to the hindquarters but was present overall as evidenced by prolonged rapid movement of pinnae to touch.

Effects of i.t. SST on nociception and motor function are summarized in Figure 4. No effects on pain behavior or motor function were observed following the administration of saline or 5 μg SST i.t. In contrast, injection of 50 μg SST i.t. caused rapid onset hind leg flaccidity in all mice examined (N = 7). Concurrently, significant increases in tail flick and hot plate response latencies were observed, which, however, were not representative of increased pain thresholds due to the motor deficit. Hindleg motor function recovered in all mice within 30 minutes following injection. With regained motor function, tail flick and hot plate response latencies were not different from baseline values. Throughout the following six-day observation period, mice continued to exhibit normal behavior.

Saline-treated mice showed normal morphology and no signs of demyelination (Figure 5A), except for one animal which exhibited a circumscribed lesion in the white matter with inflammatory response, possibly the result of mechanical damage of this area caused by the percutaneous needle injection. Three
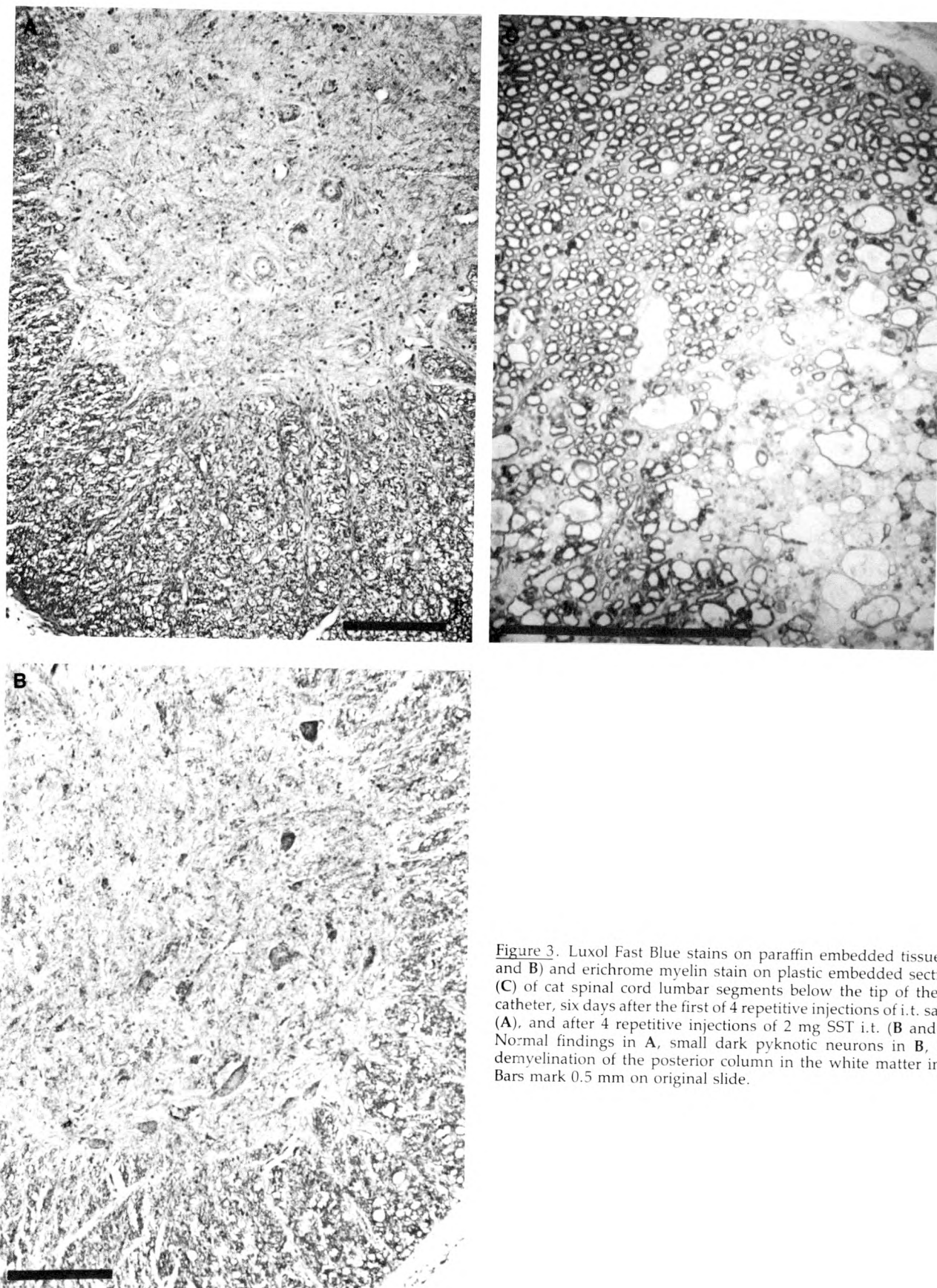
Figure 3. Luxol Fast Blue stains on paraffin embedded tissue (A and B) and erichrome myelin stain on plastic embedded sections (C) of cat spinal cord lumbar segments below the tip of the i.t. catheter, six days after the first of 4 repetitive injections of i.t. saline (A), and after 4 repetitive injections of 2 mg SST i.t. (B and C). Normal findings in A, small dark pyknotic neurons in B, and demyelination of the posterior column in the white matter in C. Bars mark 0.5 mm on original slide.

Table 4. Behavioral Effects of i.t. Somatostatin in Mice

	Saline	SST, 5 μg	SST, 50 μg
Scratching/Licking	0/5	0/3	5/7*
Hyperexcitability	0/5	2/3	2/7

Occurrence of hindquarter scratching and licking 30–60 sec following i.t. injection and hyperexcitability to touch 60 sec–3 min after i.t. injection, evaluated on a +/− basis.

(* = significant difference between treatment groups analyzed by Chi-square test).

out of 7 mice injected with 50 μg SST i.t. (group I) and 1 out of 3 mice injected with 5 μg SST i.t. (group II), showed focal demyelination in the white matter of lumbar cord segments, focal invasion of inflammatory cells into the white and grey matter (Figure 5B), and evidence of neuronal degeneration. In contrast, lumbar dorsal root ganglia of mice treated with 50 μg SST i.t., appeared normal (Figure 5C).

Discussion

The present experiments demonstrate neurotoxic effects following i.t. injection of SST in mouse and cat, as evidenced by hind leg motor dysfunction and spinal cord histopathology. I.t. injection of SST often caused an initial excitatory response. Antinociceptive effects were absent in cats, and were present in mice only during the period of temporary loss of hind leg motor function. Thus, observations in cats and mice closely correspond to previous experiments in rats (8), where i.t. SST injection evoked ... initial excitatory response, subsequent hind leg motor dysfunction, and variable degrees of recovery. Also in rats, increased response latencies to nociceptive tests were observed but only at dosages which caused general hindlimb dysfunction and permanent neuronal damage as evidenced by histologic changes in the spinal cord.

Given the differences in the volume of the intrathecal space in various species, it is difficult to precisely compare the relative sensitivity to the toxic effects of SST. It appears reasonable, however, to presume that the principle parameter is the drug concentration acutely applied to a significant area of the cord surface. In the mouse, rat, and cat, i.t. injection volumes of 5 μl (14), 10 μl (15), and 200 μl (16) produce distribution of drug from approximately mid-thoracic level to the sacral cord. In previous (8) and present studies, detectable motor dysfunction occurred with i.t. administered SST at concentrations of 10μg/μl in mouse, rat, and cat. We thus conclude that the three species examined do not qualitatively differ with regard to SST toxicity, exhibiting motor
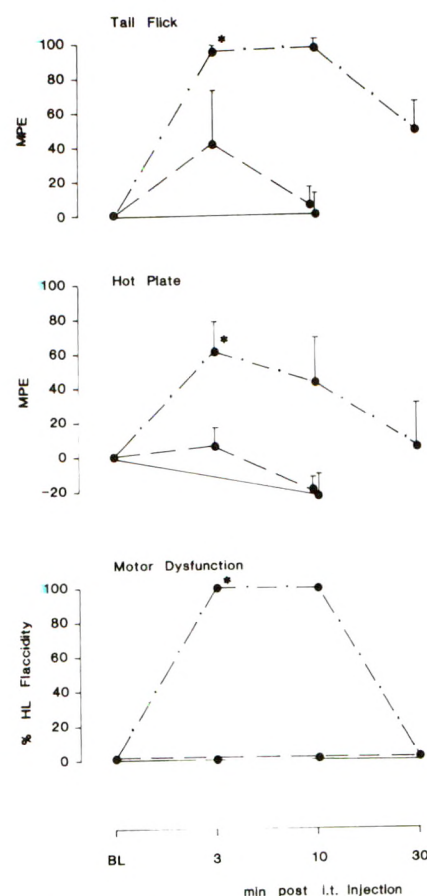
Figure 4. Effects of intrathecal (i.t.) saline (—) and somatostatin (SST) at 5 μg (− − −) and 50 μg (− · −) on tail flick and hot plate response latencies, expressed as maximum percent effect (MPE) (mean ± SE), and corresponding motor dysfunction, expressed as percent of mice showing hind leg (HL) flaccidity, at baseline (B) and 3, 10, and 30 min following i.t. injection (*$P < 0.05$ paired t-test).

impairment and histological indices of neurotoxicity. Species differences in the degree of physiological responses to i.t. SST might exist. Thus, in the present study, unlike in rats (8), SST did not produce cardiovascular collapse in mice and cats. However, valid exclusion of such events would require more extensive dose-response studies.

The present data thus contrast in part to experiments by Vaught and Scott (11), who showed that rats appeared sensitive to the paraplegic effects of an intrathecally-administered substance P analog, in contrast to mice. In those experiments, however, histological studies were not performed.

When SST was administered intrathecally in humans, it was devoid of serious side effects (1,2). This is not surprising because very low concentrations (approximately 0.08 μg/μl) were employed in humans. This concentration was below the lowest SST concentrations (1 μg/μl) administered i.t. in mice and
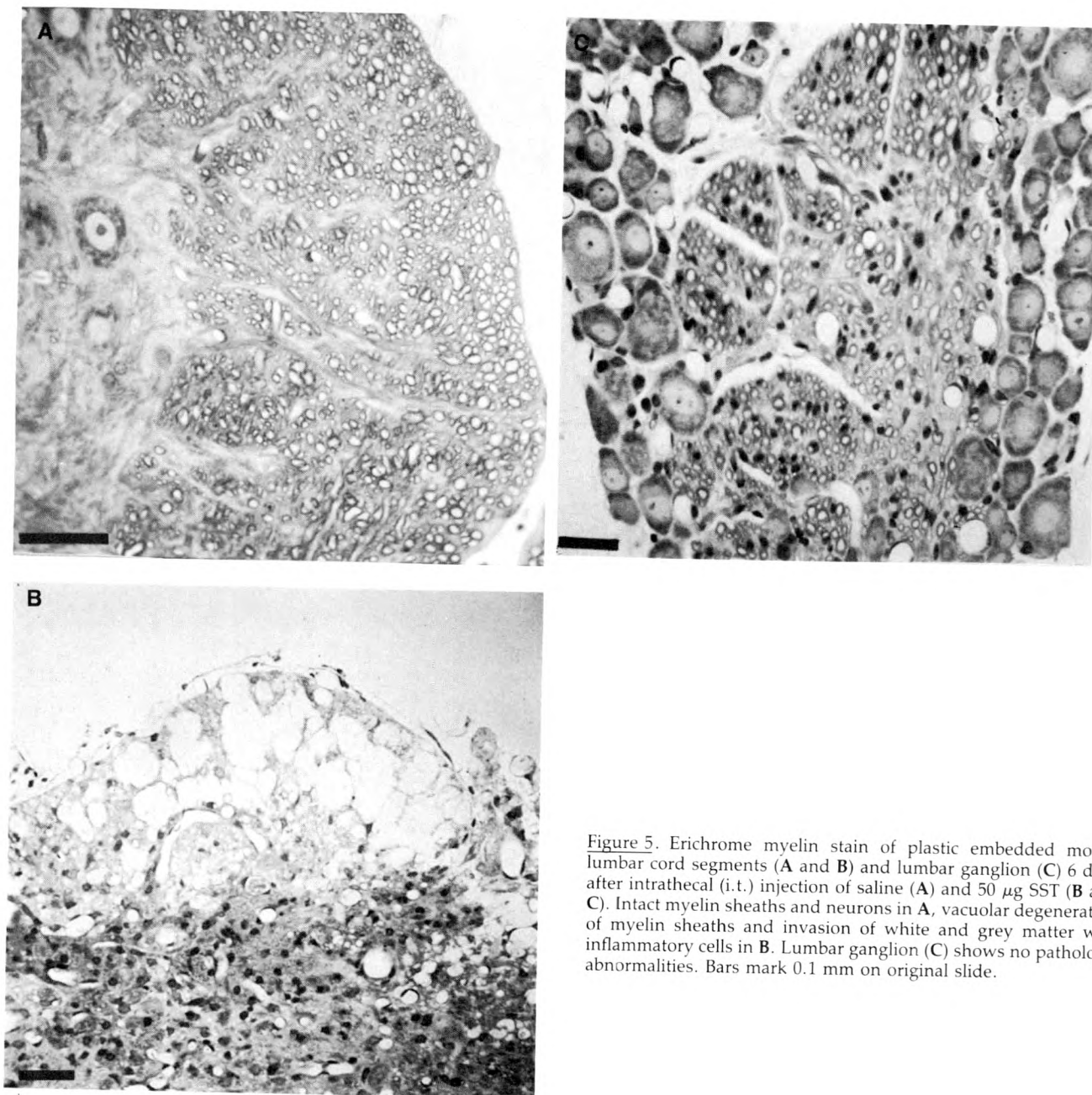
Figure 5. Erichrome myelin stain of plastic embedded mouse lumbar cord segments (**A** and **B**) and lumbar ganglion (**C**) 6 days after intrathecal (i.t.) injection of saline (**A**) and 50 μg SST (**B** and **C**). Intact myelin sheaths and neurons in **A**, vacuolar degeneration of myelin sheaths and invasion of white and grey matter with inflammatory cells in **B**. Lumbar ganglion (**C**) shows no pathologic abnormalities. Bars mark 0.1 mm on original slide.

rats (8) not causing hind leg motor dysfunction. While SST has been reported to be analgesic in man (1,2), this peptide was devoid of analgesic effects in cats, and in mice and rats (8) at doses other than those causing clear behavioral responses and motor dysfunction. It might thus be argued that the animal models employed were not sufficiently sensitive. However, the thermal tests applied (HP, TF, ST) in mouse, rat (8), and cat seem especially appropriate as SST has been associated with thermal-sensitive C-fiber afferents (17). Moreover, SST was also ineffective in blocking viscero chemical evoked nociception in rats (8).

The present experiments cannot explain analgesic effects of i.t. SST in subtoxic dosages in humans. However, in view of the minimal doses administered, placebo effects have to be considered.

Mechanisms of SST Action

The effects of intrathecally-administered SST might be attributed to direct actions on specific SST-14 receptors (18), in view of high SST tissue levels in dorsal horn segments (19) and association of SST immunoreactivity with ventral horn motor neurons

(20). However, only minimal amounts of specific SST-14 binding receptors have been observed in the rat spinal cord (18). Other possibilities of SST action include interaction with opioid receptors, where SST acts as a partial agonist-antagonist (21). Antagonistic functions to endogenous opioids, however, would counteract their antinociceptive effects (21,22). On the other hand, SST has been reported to inhibit the degradation of Leu-enkephalin, and might by this mechanism cause antinociception (23). With regard to behavioral effects of SST, peripheral sites of SST action have also to be considered (24), since similar hind limb scratching behavior was observed in mice following i.v. as well as intracranial injection (25).

Initial excitatory effects following administration of i.t. SST may explain the observed increase in epinephrine plasma levels in cats corresponding to marked sympathetic stimulation in rats (8). The sympathetic activation may represent a nonspecific stress response to i.t. SST as well as a direct effect of SST on sympathetic neurons in the intermediolateral cell column (26).

The mechanism by which SST exerts its neurotoxic effects is presently unknown, but several pathophysiologic mechanisms may be implied: 1) reduction in spinal cord blood flow (27); 2) neuronal membrane damage due to irreversible depolarization (28), and 3) changes in cell metabolism (29). Whatever the underlying pathophysiology may be, comparable neurotoxicity is observed in a variety of mammalian species following i.t. SST administration, indicating the need for caution with regard to application in humans.

References

1. Meynadier J, Chrubasik J, Dubar M, Wünsch E. Intrathecal somatostatin in terminally ill patients. A report of two cases. Pain 1985;23:9–12.
2. Chrubasik J, Meynadier J, Scherpereel P, Wünsch E. The effect of epidural somatostatin on postoperative pain. Anesth Analg 1985;64:1085–8.
3. Kuraishi Y, Hirota N, Sato Y, Hino Y, Satoh M, Takagi H. Evidence that substance P and somatostatin transmit separate information related to pain in the spinal dorsal horn. Brain Res 1985;325:294–8.
4. Murase K, Nedeljkov V, Randic M. The actions of neuropeptides on dorsal horn neurons in the rat spinal cord slice preparation: an intracellular study. Brain Res 1982;234:170–6.
5. Randic M, Miletic V. Depressant actions of methioninenkephalin and somatostatin in cat dorsal horn neurons activated by noxious stimuli. Brain Res 1978;152:196–202.
6. Wiesenfeld-Hallin Z. Intrathecal somatostatin modulates spinal sensory and reflex mechanisms: behavioral and electrophysiological studies in the rat. Neurosci Lett 1985;62:69–74.
7. Seybold VS, Hylden JLK, Wilcox GL. Intrathecal substance P and somatostatin in rats: behaviors indicative of sensation. Peptides 1982;3:49–54.
8. Gaumann DM, Yaksh TL. Intrathecal somatostatin in rats: antinociception only in the presence of toxic effects. Anesthesiology 1988;68:733–42.
9. Mollenholt P, Post C, Rawal N, Freedman J, Hökfelt T, Paulsson L. Antinociceptive and "neurotoxic" actions of somatostatin in rat spinal cord after intrathecal administration. Pain 1988;32:95–105.
10. Yaksh TL, Noueihed R. The physiology and pharmacology of spinal opiates. Ann Rev Pharmacol Toxicol 1985;25:433–62.
11. Vaught JL, Scott R. Species differences in the behavioral toxicity produced by intrathecal substance P antagonists: relationship to analgesia. Life Sci 1987;40:175–81.
12. Yaksh TL. Analgestic actions of intrathecal opiates in cat and primate. Brain Res 1978;153:205–10.
13. Bove AA, Dewey DJ, Tyce GM. Increased conjugated dopamine in plasma after exercise training. J Lab Clin Med 1984;104:77–85.
14. Hylden JLK, Wilcox GL. Intrathecal morphine in mice: a new technique. Eur J Pharmacol 1980;67:313–6.
15. Yaksh TL, Rudy T. Chronic catheterization of the spinal subarachnoid space. Physiol Behav 1976;17:1031–6.
16. Yaksh TL, Noueihed RY, Durant PAC. Studies of the pharmacology and pathology of intrathecally administered 4-anilinopiperidine analogues and morphine in the rat and cat. Anesthesiology 1986;64:54–66.
17. Wiesenfeld-Hallin Z. Substance P and somatostatin modulate spinal cord excitability via physiologically different sensory pathways. Brain Res 1986;372:172–5.
18. Srikant CB, Patel YC. Somatostatin receptors. Adv Exp Med Biol 1985;188:291–304.
19. Massari VJ, Tizabi Y, Park CH, Moody TW, Helke CJ, O'Donohue TL. Distribution and origin of bombesin, substance P and somatostatin in cat spinal cord. Peptides 1983;4:673–81.
20. Gibson SJ, Polak JM, Su H-C, et al. Distribution of substance P (SP), calcitonin gen-related peptide (CGRP), galanin (GAL), somatostatin (SOM), enkephalin (ENK), C-flanking neuropeptide Y (CPON), vasoactive intestinal polypeptide (VIP) and thyrotropin releasing hormone (TRH) in human spinal cord. Preservation of immunoreactivity in dorsal horn, autonomic nuclei and onuf's nucleus in motor neurone disease (MND). Society of Neurosci Abstract 1987;3:297.
21. Terenuis L. Somatostatin and ACTH are peptides with partial antagonist-like selectivity for opiate receptors. Eur J Pharmacol 1976;38:211–3.
22. Shook JE, Pelton JT, Lemcke PK, Porreca F, Hruby VJ, Burks TF. Mu opioid antagonist properties of a cyclic somatostatin octapeptide in vivo: identification of Mu receptor-related functions. J Pharmacol Exp Ther 1987;242:1–7.
23. Barclay RK, Phillipps MA. Inhibition of enkephalin-degrading aminopeptidase activity by certain peptides. Biochem Biophys Res Commun 1980;96:1732–8.
24. Chrubasik J, Bonath K, Cramer H, Rissler K, Wünsch E. Permeability of epidural somatostatin and morphine into the intrathecal space of dogs. Regulatory Peptides 1986;13:119–24.
25. Dobry PJK, Piercey MF, Schroeder LA. Pharmacological characterization of scratching behaviour induced by intracranial injection of substance P and somatostatin. Neuropharmacol 1981;20:267–72.
26. Holets V, Elde R. The differential distribution and relationship of serotonergic and peptidergic fibres to sympatho-adrenal

neurons in the intermediolateral cell column of the rat: a combined retrograde axonal transport and immunofluorescence study. Neuroscience 1982;7:1155–74.

27. Long JB, Martinez-Arizala A, Kraimer JM, Holaday JW. Intrathecal somatostatin causes hindlimb paralysis and reduces spinal cord blood flow in rats. Society of Neurosci Abstract 1987;13:1309.

28. Delfs JR, Dichter MA. Effects of somatostatin on mammalian cortical neurons in culture: physiological actions and unusual dose response characteristics. J Neurosci 1983;3:1176–88.

29. Unden A, Peterson LL, Bartfei T. Somatostatin, substance P, vasoactive intestinal polypeptide, and neuropeptide Y receptors: critical assessment of biochemical methodology and results. Int Rev Neurobiol 1985;27:141–77.

Lidocaine Disposition following Intravenous Regional Anesthesia with Different Tourniquet Deflation Technics

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SUKHANI R, GARCIA CJ, MUNHALL RJ, WINNIE AP, RODVOLD KA. Lidocaine disposition following intravenous regional anesthesia with different tourniquet deflation techniques. Anesth Analg 1989;68:633–7.

It has been claimed that tourniquet cycling, cyclic deflation and reinflation of the tourniquet at the termination of intravenous regional anesthesia (IVRA), enhances the safety of IVRA by minimizing the peak blood level of local anesthetics. To evaluate the validity of these claims and to determine the optimal cycling technic, peak arterial (Cmax) plasma concentrations of lidocaine were determined as well as the time to reach these peaks (Tmax) utilizing contralateral radial arterial blood samples in three groups of volunteers after 30 minutes of IVRA: In all three groups IVRA was induced with 3 mg/kg of lidocaine and maintained for 30 min. In the first group the tourniquet was then simply deflated once (and not reinflated); in the second group the

tourniquet was deflated three times with variable periods of deflation (0, 10 and 30 seconds) separated by 1-minute periods of reinflation; and in the third group the tourniquet was again deflated 3 times but with fixed periods of deflation (10 sec) separated by 1 min periods of reinflation. The results obtained indicate that cycling technics do not appear to significantly reduce Cmax, but they do significantly prolong Tmax. Of the two cycling technics, the 10-second deflation interval technic appeared to be superior, both clinically and pharmacologically, as it was associated with less venous congestion and therefore less discomfort, and it sequentially decreased the arterial plasma concentration of lidocaine with each subsequent deflation-reinflation cycle.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—intravenous. PHARMACOKINETICS—intravenous regional anesthesia. ANESTHETICS, LOCAL—lidocaine.

Intravenous regional anesthesia (IVRA) is widely utilized for minor surgical procedures on the extremities, especially the upper extremities, because of its safety, simplicity and high rate of success. Nonetheless, systemic toxic reactions and even deaths have been reported with IVRA, the majority of which have been attributable to a high systemic concentration of local anesthetic following deflation of the tourniquet (1–3). It was originally suggested by Bier (4) and more recently by Holmes (5) that such high blood levels might be prevented by cyclic deflation and reinflation of the tourniquet at the end of the surgical procedure. The present study was carried out in an attempt to document 1) whether cyclic deflation and reinflation of the tourniquet at the end of the surgical procedure

is, in fact, superior to the traditional single deflation technic by preventing or decreasing elevated blood levels of the local anesthetic; and 2) whether the time interval between each deflation and reinflation has a significant impact on the resultant levels.

Most of the studies of the blood levels of local anesthetic resulting from intravenous regional anesthesia have reported venous levels of lidocaine drawn from the contralateral extremity and have attempted to correlate them with the clinical signs of systemic toxicity (6–9). Eriksson (10) and Hargrove (11), and their associates, on the other hand, reported arterial levels suggesting that the arterial levels of a local anesthetic would correlate better with systemic toxicity than the venous levels, since arterial blood contains the same amount of local anesthetic as the blood reaching the brain and the heart. Therefore, in the present study the concentration of lidocaine in the arterial blood drawn from the contralateral extremity was utilized to compare the safety of the different technics of tourniquet release.

Methods and Materials

After approval by our Human Research Committee, 15 healthy, consenting, unpremedicated, adult volunteers were divided into three groups on the basis of the type of tourniquet deflation technic to be utilized to terminate IVRA.

In Group I (non-cyclic deflation) the tourniquet was deflated only once and was not reinflated. In Group II (cyclic deflation-variable deflation interval) the tourniquet was deflated three times in a cyclic manner with progressively increasing periods of deflation, 0, 10, and 30 seconds respectively, separated by fixed 1-minute periods of reinflation. In Group III (cyclic deflation-fixed deflation interval) the tourniquet was deflated three times in a cyclic manner, but with fixed 10 second periods of deflation separated by fixed 1-minute periods of reinflation.

In all three groups, following the application of automatic blood pressure and ECG monitors, the contralateral radial artery was cannulated. In addition, a 20-gauge catheter was placed in the vein on the dorsum of the hand of the extremity to be anesthetized, and a single-cuff pneumatic tourniquet was placed on the middle of the upper arm over protective Webril gauze and connected to an ATS 1000 Tourniquet System (Aspen Labs Inc., Littleton, Colorado). The arm was then elevated and drained of blood by tightly wrapping the arm with an Esmarch bandage from the fingertips to the level of the tourniquet, which was then inflated to a pressure of 250 mm Hg. After removal of the Esmarch bandage, 3.0 mg/kg of lidocaine 0.5% (Xylocaine® 0.5% for local infiltration and intravenous regional anesthesia) was injected over 2 minutes into the intravenous catheter on the dorsum of the hand. Upon completion of the injection a stopwatch was started: 30 min following the injection of the local anesthetic, the tourniquet was deflated using one of the three technics under study.

In all three groups of patients arterial blood samples were drawn from the radial artery prior to the initial deflation of the tourniquet to determine baseline levels of lidocaine. Then, following deflation of the tourniquet, arterial samples were drawn as follows: In Group I the samples were drawn 15, 30, 45 seconds and 1, 1½, 2, 3, 5, 10, 20, and 30 minutes after deflation. In Groups II and III, while the various deflation and reinflation cycles were carried out, samples were drawn every 15 seconds for the first 4 minutes, and then 4½, 5, 6, 7, 8, 9, and 10 minutes after the initial deflation.

As soon as the samples of arterial blood were drawn, they were immediately centrifuged and the

Table 1. Patient Characteristics

	Group I (n = 5)	Group II (n = 5)	Group III (n = 5)
Age (yr)	30.6 ± 3.6	31.0 ± 2.6	29.6 ± 2.9
Weight (kg)	71.2 ± 9.0	70.8 ± 6.6	80.1 ± 4.1
Height (inches)	69.0 ± 0.4	68.0 ± 4.1	72.0 ± 2.0
Arterial Parameters			
Cmax (µg/ml)	4.7 ± 1.5	4.3 ± 0.9	4.0 ± 0.6
Tmax (sec)	54.0 ± 25.0	225.0 ± 69.0*	300.0 ± 37.0*

*Statistically significantly longer than Group I $P < 0.05$.
Data are mean ± SD.

serum analyzed for lidocaine levels within 48 hours of collection, using fluorescence polarization immunoassay (12,13) (TDxR Abbott Laboratories, Diagnostic Division, Irving, Texas). The intra- and interday coefficients of variation for the assay with replicate control sample(s) were less than 5%; sensitivity of the assay was 0.05 µg/ml.

The peak lidocaine concentration (Cmax) and the time to peak lidocaine concentration (Tmax) were determined by inspection of the arterial concentration-time curves plotted for each subject. In addition, to compare the effect of each of the three cycling technics on arterial lidocaine levels, peak lidocaine levels were also examined following each deflation in each volunteer in Groups II and III. Verbal contact was maintained with all subjects throughout the study to monitor any and all symptoms that might be related to the systemic effects of the lidocaine.

The data were analyzed using a two way analysis of variance, and when indicated, multiple comparisons were made for Groups II and III versus Group I, using a distribution-free, multiple comparison test based on Friedman rank sums (14). Statistical significance was assumed with $P < 0.05$.

Results

The volunteers in the three groups were not statistically significantly different with respect to age, weight or height (Table 1). In all instances control arterial blood samples drawn prior to tourniquet deflation had plasma lidocaine concentrations less than 0.05 µg/ml, indicating a negligible leakage of local anesthetic under the tourniquet or via the circulation in the humerus.

Figure 1 displays the mean arterial lidocaine concentrations plotted against time for each tourniquet deflation technics. In Group I arterial lidocaine levels peaked early after deflation; in Group II they reached progressively higher peaks after each deflation; and in Group III, arterial lidocaine levels reached progres-
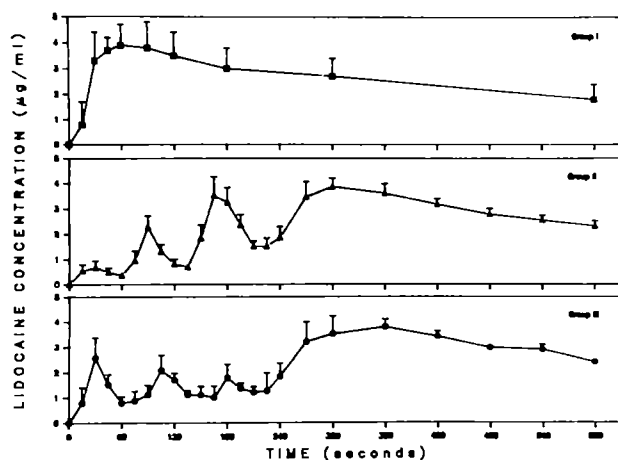
Figure 1. Time course of arterial plasma levels of lidocaine in μg/ml (mean ± SEM) resulting from the three technics of tourniquet deflation. Maximal arterial lidocaine levels did not differ significantly between the three groups. The arterial samples were drawn from the contralateral radial artery.
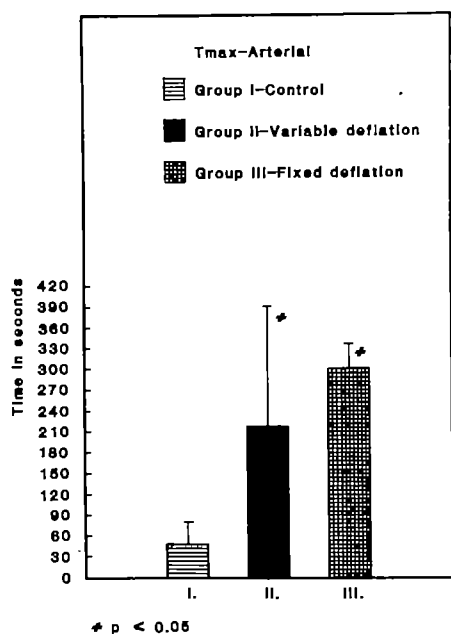
Figure 2. Time (seconds: mean ± SEM) to maximum arterial concentrations of lidocaine in the three groups. Tmax arterial was significantly longer in both Groups II and III than in Group I; there was no significant difference between Groups II and III.

sively lower peaks after each deflation until the final deflation, when the final peak level was virtually identical to the maximal level achieved in both Groups I and II. There were no statistically significant differences between the three groups with respect to arterial Cmax (Table 1).

Figure 2 represents Tmax, the mean time to the maximum arterial lidocaine concentration for each deflation technic. Tmax was significantly greater in both Groups II and III than in Group I, but Groups II

and III did not differ significantly from each other (Table 1).

Table 2 and Figure 3 represent Cmax, the peak arterial lidocaine levels that followed each deflation of the tourniquet in Groups II and III. Because the first deflation-reinflation interval was zero in Group II and 10 seconds in Group III, significantly higher lidocaine levels resulted in Group III. The second deflation-reinflation interval was 10 seconds in both groups, so the lidocaine levels that resulted from the second cycle were almost identical in the two groups. The third deflation-reinflation interval was 30 seconds in Group II and 10 seconds in Group III, so, as might be expected, the lidocaine levels that resulted from the third cycle were higher in Group II than in Group III, but this difference was not significantly different. Finally, the last deflation resulted in almost identical blood levels in both Groups II and III; and in both these groups lidocaine levels peaked 15–45 seconds following initiation of each deflation.

Two volunteers, both in Group I, complained briefly of dizziness and ringing in the ears, but these symptoms lasted less than a minute and were without sequelae. None of the volunteers in Groups II and III reported any symptoms of toxicity.

Discussion

The toxicity of local anesthetic agents depends upon the arterial plasma concentration, regardless of the route of administration. Venous plasma levels of lidocaine following tourniquet deflation after intravenous regional anesthesia have been extensively studied in the past, most of the studies indicating that the signs and symptoms of systemic toxicity appear at venous levels of 5 μg/ml or greater (6–8). Arterial levels of lidocaine following intravenous regional anesthesia have not been studied as extensively, and, therefore, the correlation between arterial levels and the signs and symptoms of toxicity under clinical conditions has not yet been established. Theoretically, the arterial plasma level of a local anesthetic should correlate better with the clinical signs and symptoms of toxicity than the venous level, since the arterial level represents the concentration of the local anesthetic agent to which the heart and brain are exposed. All four of the previous studies which measured arterial levels of lidocaine after IVRA (9–11,15) measured the levels following a single deflation of the tourniquet, and all four studies found that the arterial plasma concentrations of lidocaine reach a peak of 4–6 μg/ml 30–60 seconds after tourniquet deflation. Our studies utilizing a single deflation

Table 2. A Comparison of Peak Lidocaine Levels Following Each Deflation With the Two Technics of Cyclic Deflation/Reinflation

	Arterial Lidocaine Level in $\mu g/ml$							
	Group II				Group III			
Volunteers (Number)	Deflation Cycle				Deflation Cycle			
	1	2	3	Final	1	2	3	Final
1	1.23	3.16	5.58	4.92	1.35	0.5	0.54	3.31
2	0.5	1.9	1.9	3.3	3.5	1.8	1.7	3.9
3	0.43	1.22	2.61	3.19	4.5	4.0	3.2	4.6
4	0.01	1.87	2.93	3.85	3.3	1.4	1.0	3.1
5	1.26	3.28	4.43	4.13	0.5	2.27	2.3	4.1
Mean	0.68	2.28	3.52	3.87	2.59*	2.08	1.79	3.80
±	±	±	±	±	±	±	±	±
S.D.	0.54	0.89	1.51	0.69	1.59	1.33	1.06	0.60

In both Groups II and III the peak lidocaine levels occurred 15–45 sec following each deflation.
*Level significantly higher than in Group II.
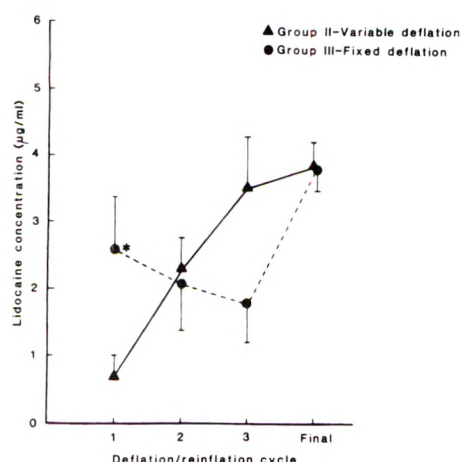
Figure 3. Peak arterial plasma levels of lidocaine in $\mu g/ml$ (mean ± SEM) with each deflation/reinflation cycle in Groups II and III. In Group II the arterial lidocaine level began low and gradually increased following each deflation, while in Group III it began higher but declined following each deflation until the final deflation, after which it reached the same peak as Group II. The first deflation resulted in a significantly higher arterial lidocaine level in Group III than in Group II, but this level was below the toxic range.

technic (Group I) yielded almost identical results. Eriksson et al. (10) also demonstrated that EEG changes and symptoms of toxicity appear at arterial plasma levels of lidocaine greater than 4 $\mu g/ml$. In our study the only two volunteers who reported symptoms of toxicity had arterial lidocaine levels of 5.8 $\mu g/ml$ and 4.4 $\mu g/ml$ and were members of Group I where cycling was not utilized. In Groups II and III, where tourniquet deflation and reinflation was cycled, although arterial levels similar to those seen in Group I were achieved, none of the volunteers reported any symptoms suggestive of toxicity.

Our data comparing arterial levels of lidocaine in the three groups indicated that although there were no significant differences in the Cmax arterial produced by the three technics of tourniquet deflation, arterial Tmax was significantly longer in volunteers in whom the tourniquet was cycled, regardless of the technic of cycling. Both Bromage (6) and Hargrove (11) and their associates demonstrated independently that the Cmax of a local anesthetic is of less importance in terms of the toxicity than the time over which this maximum level is achieved and the duration it is maintained. If such is the case, then our study explains why the only two patients who were symptomatic were in Group I and suggests that tourniquet cycling is the safest technic for terminating intravenous regional anesthesia.

Following intravenous regional anesthesia the local anesthetic agent is only released after deflation of the tourniquet, so the time interval between deflation and reinflation becomes critical, as it limits the amount of drug that enters the systemic circulation. Both Salo et al. (16) and Merrifield and Carter (17) compared venous blood levels drawn from a contralateral arm vein after single deflation and cyclic deflation/reinflation technics. While Salo et al. reported no significant difference in the venous levels resulting from the two technics, Merrifield and Carter found that cycling resulted in a significant reduction in the venous levels of the local anesthetic. The differences in these two reports are undoubtedly due to a difference in the cycling technics utilized.

Thorn-Alquist (15) found that following tourniquet deflation the peak arterial plasma levels of lidocaine occurred at 15 seconds, and it was this observation that led the present investigators to conclude that the ideal deflation interval between two reinflations should probably be less than 15 seconds. However,

while carrying out the present study we found that if the interval between deflation and reinflation is too short (deflation and immediate reinflation) venous congestion results, and this causes significant discomfort in the extremity that is no longer fully anesthetized. Salo et al. (16) also reported that venous congestion occurs if the deflation interval between two reinflations was 5 sec or less. However, they also indicated that, more important than the discomfort, was the fact that while very little drug was released during such a short deflation, the congestion it caused resulted in a rapid washout of the local anesthetic from the arm and produced high levels of local anesthetic with the next deflation. We noted similar findings: the lowest lidocaine levels resulted when the deflation interval was zero (Group II—first deflation-reinflation cycle), whereas the highest levels resulted when the deflation interval was 30 seconds (Group II—third deflation-reinflation cycle). Clearly, the blood level is directly proportional to the interval of deflation. Therefore, our data support the conclusion of Merrifield and Carter (17) (based on venous blood levels) that a deflation interval of 10 sec appears to be the best compromise, both clinically and pharmacokinetically: the volunteers reported no discomfort due to venous congestion with this interval, and yet progressively decreasing arterial levels resulted with each subsequent deflation, except for the last (Figs. 1, 3).

To summarize, the data obtained in the present study indicate that while cyclic, intermittent deflation and reinflation of the tourniquet following intravenous regional anesthesia does not reduce Cmax, it significantly prolongs Tmax. Furthermore, our data indicate that both in terms of arterial levels of the local anesthetic and in terms of patient comfort, the optimal deflation-reinflation cycle is one that allows an interval of 10 sec between each deflation and reinflation. Finally, our data support the suggestion of Salo et al. that "to achieve an accurate deflation-reinflation cycle and to avoid unnecessary manipulations, an automatic deflation-reinflation mechanism should be built into the tourniquet regulators used for intravenous regional anesthesia."

References

1. Kennedy BR, Duthie AM, Parbrook GD. Intravenous regional analgesia: An appraisal. Br Med J 1965;1:954–7.

2. Cox JMR. Intravenous regional analgesia. Can Anaesth Soc J 1964;11:503–8.

3. Heath ML. Deaths after intravenous regional anaesthesia. Br Med J 1984;285:913–4.

4. Bier A. On local anaesthesia with special reference to vein anaesthesia. Edinburgh Med J 1910;5:103–23.

5. Holmes CM. Intravenous regional analgesia. Lancet 1963;1:245–7.

6. Bromage PR, Robson GJ. Concentration of lidocaine in the blood after intravenous, intramuscular epidural and endotracheal administration. Anaesthesia 1961;16:461–78.

7. Foldes FF, Molloy R, McMall PG, Koukal LR. Comparison to toxicity of intravenously given local anesthetic agents in man. JAMA 1960;172:1492–8.

8. Mazze RI, Dunbar RW. Plasma lidocaine concentrations after caudal, lumbar epidural axillary block and intravenous regional anesthesia. Anesthesiology 1966;27:574–9.

9. Tucker GT, Boas RA. Pharmacokinetic aspects of intravenous regional anesthesia. Anesthesiology 1971;34:538–49.

10. Eriksson E, Persson A, Ortengreu B. Intravenous regional anesthesia—an attempt to determine the safety of the method and comparison between prilocaine and lidocaine. Acta Chir Scand Suppl 1966;358:47–54.

11. Hargrove RL, Hoyle JR, Beckett AH. Blood levels of local anaesthetics following intravenous regional anaesthesia. Acta Anaesthesiol Scand Suppl 1969;36:115–20.

12. Jolley ME. Fluorescence polarization immunoassay for determination of therapeutic drug levels in human plasma. J Analytical Toxicol 1981;5:236–40.

13. Jolley ME, Stroupe SD, Schwenzer KS, Wong CHJ, Lu-Steffes M, Hill HD, Popelka SR, Holen JT, Kelso DM. Fluorescence polarization immunoassay III. An automated system. Clin Chem 1981;27:1575–9.

14. Hollander M, Wolfe DA. The Two Way Layout. In: Nonparametric Statistical Methods. John Wiley Publishers, 1973:138–55.

15. Thorn-Alquist AM. Blood concentrations of local anesthetics after intravenous regional anaesthesia. Acta Anaesthesiol Scand 1969;13:229–40.

16. Salo M, Kanto J, Jalonen J, Lawrikainen E. Plasma lidocaine concentrations after different methods of releasing the tourniquet during intravenous regional anesthesia. Ann Clin Res 1979;11:164–8.

17. Merrifield AJ, Carter SJ. Intravenous regional analgesia: Lignocaine blood levels. Anaesthesia 1965;20:287–93.

Species Variation in the Site and Mechanism of the Neuromuscular Effects of Diadonium in Rodents

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The unusually wide, 80-fold species variation observed by others (1,2) in the neuromuscular (NM) potency of diadonium, a nondepolarizing muscle relaxant (MR), between cat and man suggested that the site and mechanism of its NM effect may vary in different species. To obtain information on this question, the NM potency of diadonium and the reversibility of its NM effect by neostigmine and/or 4-aminopyridine (4AP) was investigated on the in vitro phrenic nerve—hemidiaphragm preparations of rats, mice and guinea pigs. The concentration of diadonium that caused 90% NM block (IC90) was much greater in guinea pigs, 1.74 ± 0.02 and 1.28 ± 0.01 μ, when the preparations were stimulated with single stimuli at 0.1 Hz or with 0.1 s trains of 50 Hz tetani every 10 s, respectively, than in rats (IC90 = 62.4 ± 0.89 and 52.1 ± 1.00 μM) or mice (IC90 = 51.9 ± 0.98 and 44.4 ± 0.22 μM). In guinea pigs, the NM blocking effect of diadonium could be antag-

onized by neostigmine. This indicates that in this species the NM blocking effect of diadonium is primarily caused by inhibition of the interaction of acetylcholine (ACh), released by the nerve impulse, with the cholinergic receptors (cholinoceptors) of the postjunctional membrane (p.j.m.). By contrast, in rats and mice diadonium was not antagonized by neostigmine but was reversed by 4-aminopyridine. This suggests that in these species, in contrast to other nondepolarizing MR, diadonium does not inhibit NM transmission postsynaptically, but by inhibiting the positive nicotinic feedback mechanism of mobilization of ACh from reserve depots to release sites, causes a presynaptic NM block. The different sites and mechanisms of the diadonium block in guinea pigs on one hand, and in rats and mice on the other, are probably caused by differences in the interaction of diadonium and the ACh recognition sites of the cholinoceptors of the p.j.m. in the 3 species. No similar species variation could be demonstrated in the sites and mechanisms of any of the nondepolarizing MR in clinical use.

Key Words: NEUROMUSCULAR RELAXANTS—diadonium.

Diadonium [bis-(1-adamantyl-dimethylammonium-ethyl)-succinate·ditosylate] (Fig. 1) is a bisquaternary ammonium compound containing two ester linkages.

It has been reported that on i.v. administration 0.13 to 0.18 mg/kg diadonium causes "head drop" in rabbits; its apneic dose was 2.9 to 4.7 mg/kg in mice; and 0.25 to 0.35 mg/kg produced complete block of NM transmission in anesthetized cats (1). The clinical pharmacology of diadonium was investigated by Bu-

natian (2). He found that 10 to 15 mg/kg diadonium was required to facilitate tracheal intubation. These doses of diadonium caused moderate hypotension and mydriasis. The duration of action of diadonium was similar to that of succinylcholine (numerical data not furnished). The first administration of half the initial dose provided relaxation for 10 to 12 minutes. The duration of action of subsequent maintenance doses became progressively longer.

Our interest in diadonium was aroused by the unusually wide species variation of its NM potency. Approximate relative potencies are: rabbit 80, cat 40, mouse 4, and human 1 (1,2). It seemed possible that this unusually wide species variation in the NM effect of diadonium is not only quantitative, but that the

$(CH_3)_2 N-(CH_2)_2-OOC-(CH_2)_2-COO-(CH_2)_2-N(CH_3)_2 \cdot 2SO_3C_6H_4CH_3$

M. w. 873. 0.8.
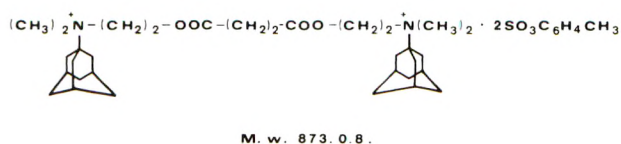
Figure 1. The structural formula of diadonium.

site and/or mechanism of the NM effects of diadonium may be different in various species.

Considerable information can be obtained regarding the site and mechanism of the NM effect of compounds by measuring their NM potency at low and high frequency stimulation (3) and by observing the antagonist effect of cholinesterase inhibitors (anticholinesterases; anti-ChE) and 4-aminopyridine (4AP) on the NM block (4–6). Anti-ChE only antagonize the NM effect of compounds which produce NM block by prevention of the interaction of acetylcholine (ACh) released by the nerve impulse with the nicotinic receptors (cholinoceptors) of the postjunctional membrane. Anti-ChE cause little or no antagonism of the NM block caused by compounds, such as hexamethonium, which inhibit the mobilization of ACh to sites where they are readily available for release by the nerve impulse (3) or by others like Mg^{2+} (7) or neomycin (5) which inhibit the release of ACh. These two types of block, however, are antagonized by 4AP (5,8) and related compounds.

The objective of the present study was to investigate the site(s) and mechanism(s) of the NM blocking effect of diadonium in rats, mice, and guinea pigs.

Methods

The experiments were carried out on the phrenic nerve-hemidiaphragm of 275–350 g male Sprague-Dawley rats, 25–30 g Webster mice, and 350–400 g Harley guinea pigs. Animals were lightly anesthetized with ethyl ether and decapitated. The costal end of the preparations were fixed to the bottom of an organ bath, its tendon was fixed to an FT03 transducer, and the phrenic nerve was placed on bipolar platinum electrodes immersed in the bath filled with a modified Krebs' solution, containing instead of 2.5 mM $CaCl_2$ and 1.2 mM $MgSO_4$, 1.4 mM $CaCl_2$ and 0.9 mM $MgSO_4$. The $[Ca^{2+}]$ 1.1 mM and $[Mg^{2+}]$ 0.8 mM in this solution was the same as that of rat or human plasma (9). The bath temperature was kept at 37°C and, when aerated with 95% O_2–5% CO_2, its pH was 7.38–7.42.

In most experiments the preparations were stimulated (with a Grass Model 88 stimulator) through the phrenic nerve with supramaximal, square wave impulses of 0.2 ms duration administered either at 0.1 Hz ("twitch" stimulation) or every 10 seconds with 0.1 second trains of 50 Hz impulses ("tetanic" stimulation). The optimal resting tension of the hemidiaphragms, 10–12 g in rats and guinea pigs and 1.5–2.0 g in mice, was determined at the start of each experiment. The force of contraction (designated P with twitch and P_o with tetanic stimulation) was quantitated with FT03 transducers and continuously recorded on a Grass Model 79D polygraph. The concentrations of diadonium, which reduced P or P_o to 50% (IC50) or 90% (IC90) of control, were determined from computer derived, best fit, log dose-response regression lines in at least 12 experiments for each species. In 4 experiments, within each species, diadonium block greater than 90% was established and the recovery of P and P_o was observed after washout, and after increasing the $[CaCl_2]$ to 2.5 mM, thereby elevating the $[Ca^{2+}]$ to 2.0 mM, or after the addition of 0.75 μM neostigmine methylsulfate or 40 μM 4AP to the bath. In other experiments preparations were stimulated for short periods sequentially at 0.1, 1.0, 2.0, 3.0, 5.0 and Hz before and after 20% diadonium block of P was induced at 0.1 Hz.

The effect of diadonium on the force of contraction of completely curarized and directly stimulated preparations (supramaximal impulses of 2 ms duration at 0.1 Hz) was also investigated.

The hydrolysis rate of diadonium by human red cell acetylcholinesterase (AChE; EC 3·1·1·7) and plasma butyrylcholinesterase (BuChE; EC 3·1·1·8) was investigated by a null-point, potentiometric, titrimetric method (10) using a pH-Stat (Radiometer, Copenhagen). The substrate concentration of diadonium in these determinations varied between 10^{-5} M and 0.5×10^{-3} M. The highest concentration was selected because it approximates the plasma concentration expected to be present immediately after the i.v. injection of a 15 mg/kg intubating dose of diadonium in human subjects.

The inhibitory effect of diadonium on the hydrolysis of 3×10^{-3} M acetyl-β-methylcholine (MeCh) by AChE and that of 2×10^{-2} M butyrylcholine (BuCh) by BuChE were also measured. These substrate concentrations were found to be optimal in earlier studies (11). In addition the inhibitory effect of diadonium on the hydrolysis of ACh by homogenized rat or guinea-pig diaphragm were also determined.

The results were statistically analyzed with ANOVA followed by Tuckey's test (12), Student's t-test or paired t-test, as appropriate; $P < 0.05$ was considered statistically significant.

Table 1. The In Vitro Neuromuscular Potency of Diadonium in Rat, Mouse and Guinea Pig*

Species	Stimulation	Number of Experiments	I50 (μM)	I90 (μM)
			(Mean ± SEM)	
Rat	Twitch	22	47.4 ± 0.70	62.4 ± 0.89
	Tetanus	26	31.4 ± 0.55	52.1 ± 1.00
Mouse	Twitch	16	38.3 ± 1.02	51.9 ± 0.98
	Tetanus	12	25.2 ± 0.22	44.4 ± 0.22
Guinea Pig	Twitch	16	1.22 ± 0.01	1.74 ± 0.02
	Tetanus	12	0.98 ± 0.01	1.28 ± 0.01

*For statistical significance of data see Results.

Results

Diadonium, 100 μM, had no effect on the force of contraction of the completely curarized, directly stimulated preparations.

Observations summarized in Table 1 indicate that with twitch stimulation, diadonium is about 35 and 30 times more potent in guinea pigs than in rats and mice, respectively. During tetanic stimulation it is 40 and 35 times more potent in the guinea pigs than in rats and mice. The potency ratio between mice and rats was 1.20 with both types of stimulation. The differences in the IC50 and IC90 values between any two of the three species were significant. The potency of diadonium was significantly greater with tetanic than with twitch stimulation in all 3 species.

After washout, both P and P_o rapidly returned close to or above control levels in all 3 species (Table 2). Recovery rate (time for recovery of force of contraction from 25–75% of control) of P was significantly more rapid in mice than in rats or guinea pigs and faster in rats than in guinea pigs. The recovery rate of P_o was significantly faster in mice than in rats or guinea pigs and similar in rats and guinea pigs. Recovery rate of P was also significantly faster than that of P_o in rats and guinea pigs, but not in mice.

Increasing the $[Ca^{2+}]$ of the bath from 1.1 to 2.0 mM, resulted in only partial recovery of P. The recovery was similar in rats and guinea pigs but significantly less in mice. The recovery of P_o (only investigated in rats) was also significantly less than that of P.

Neostigmine 0.75 μM did not antagonize the greater than 90% diadonium block in rats and mice but rapidly returned both P and P_o to control in guinea pigs (Fig. 2 and Table 2). 4AP, 40 μM, returned P in all 3 species and P_o in guinea pig to above control values. In rats and mice, however, 4AP only partially antagonized P_o.

In both rats and guinea pigs the steady state 20% NM block caused by diadonium or d-tubocurarine became progressively greater ($P < 0.02$) as the stim-

ANTAGONISM OF THE DIADONIUM BLOCK IN VITRO
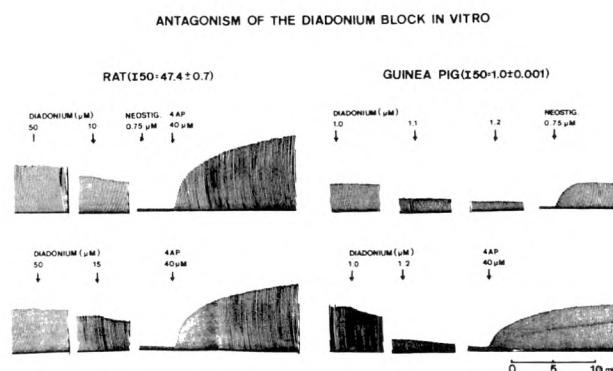
Figure 2. Antagonism of diadonium block by neostigmine or 4AP in the phrenic nerve—hemidiaphragm preparations of rats and guinea pigs. Note that 4AP antagonized the NM block in both species. Neostigmine, however, only reversed the diadonium block in guinea pigs.

ulus frequency increased from 0.1 to 5.0 Hz (Table 3). Increasing the stimulation rate caused an increase in the intensity of both diadonium and d-Tc block in guinea pigs, that was significantly greater than in rats, except that at 5 Hz the difference in the intensity of the diadonium block in rats and guinea pigs was not significant.

The increase in the intensity of the diadonium block caused by increasing stimulation rates could be prevented by 4AP in all 3 species (Figs. 3 and 4). Neostigmine, however, prevented this effect only in guinea pigs (Fig. 4).

Diadonium was not hydrolyzed by either human plasma BuChE or human red cell AChE. The inhibitory effect of diadonium on various cholinesterases is summarized in Table 4.

Discussion

The characteristics of the diadonium induced NM block in guinea pigs on one hand, and in rats and mice on the other hand, were found to be dissimilar. In guinea pigs the diadonium block, similar to the d-Tc block (13), could be antagonized by neostigmine.

Table 2. Antagonism of the Greater Than 90% Diadonium Block by Washout, Increasing [Ca^{2+}], Neostigmine or 4-Aminopyridine*

Species	Stimulation	After Washout		After CaCl$_2$		After 4-Aminopyridine		After Neostigmine	
		Recovery Rate (min)	Maximal Recovery (%)	Recovery Rate (min)	Maximal Recovery (%)	Recovery Rate (min)	Maximal Recovery (%)	Recovery Rate (min)	Maximal Recovery (%)
Rat	Twitch	1.55 ± 0.32†	106.1 ± 1.4	—‡	56.7 ± 4.2	1.96 ± 0.23	168.0 ± 4.20		
	Tetanus	4.67 ± 0.26	99.7 ± 1.9	—	27.3 ± 2.2	—	56.6 ± 3.07	In rat and mouse no recovery after neostigmine.	
Mouse	Twitch	0.26 ± 0.02	104.7 ± 1.4	—	23.0 ± 2.1	1.1 ± 0.10	121.7 ± 2.8		
	Tetanus	0.50 ± 0.18	124.1 ± 2.5	Not investigated		—	31.4 ± 1.1		
Guinea pig	Twitch	2.71 ± 0.14	110.8 ± 2.08	—	48.2 ± 2.3	1.7 ± 0.10	214.2 ± 4.10	1.5 ± 0.79	100.1 ± 3.89
	Tetanus	4.62 ± 0.22	103.9 ± 2.27	Not investigated		9.6 ± 1.37	104.9 ± 2.64	1.2 ± 0.11	109.8 ± 2.51

*For statistical significance of data see Results.
†All values are means ± SEM of 4 experiments.
‡Broken lines indicate that since maximal recovery was <75%, recovery rate could not be determined.

Table 3. The Influence of Stimulation Rate on the Intensity of the Steady State Diadonium or D-Tubocurarine Block in Rats and Guinea Pigs*

Species	Muscle Relaxant	Neuromuscular Block (%) With Stimulation Rates (Hz) of				
		0.1	1.0	2.0	3.0	5.0
Rat	Diadonium	21.0 ± 1.2†	28.2 ± 1.5	40.5 ± 2.2	61.1 ± 2.4	77.7 ± 2.2
	d-Tc	21.4 ± 1.0	31.4 ± 1.6	41.8 ± 1.7	49.5 ± 1.6	70.0 ± 1.1
Guinea pig	Diadonium	20.0 ± 0.5	43.2 ± 4.3	61.7 ± 2.1	71.9 ± 1.6	79.4 ± 1.4
	d-Tc	20.0 ± 0.7	40.0 ± 2.7	60.0 ± 2.3	68.7 ± 2.3	76.2 ± 2.4

*For statistical significance of data see Results.
†All data are means ± SEM of 4 experiments.
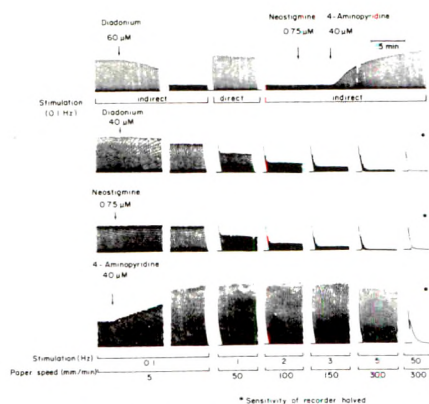
Figure 3. The influence of neostigmine and 4-aminopyridine (4AP) on the greater than 90% diadonium block and on the increase of the intensity of the partial diadonium block caused by increasing stimulation rates in the phrenic nerve—hemidiaphragm preparation of rats. Note that neostigmine did not reverse the diadonium block and did not prevent the deepening of the NM block caused by increasing stimulation rates. 4AP antagonized the diadonium block and prevented the effect of increasing stimulation rates on the intensity of the block.

Figure 4. The influence of neostigmine and 4-aminopyridine (4AP) on the greater than 90% diadonium block and on the increase of the intensity of the partial diadonium block caused by increasing stimulation rates in the phrenic nerve—hemidiaphragm preparation of guinea pigs. Note that both neostigmine and 4AP antagonized the diadonium block and prevented the effect of increasing stimulation rates on the intensity of the block.

In this species neostigmine also antagonized the greater than 90% diadonium block and prevented progression of the intensity of the NM block caused by increasing stimulation rates (Fig. 4). The characteristics of the diadonium block in rats and mice, in this study, were found to be different from those of a typical nondepolarization block. Increasing stimulation rates increased the intensity of the NM block indicating that diadonium has a presynaptic inhibitory effect. However, neostigmine did not antagonize either the 20% or the greater than 90% diadonium block and did not prevent the effect of increasing stimulation rates on the intensity of the NM block (Fig. 3). The NM effects of diadonium and the influ-

Table 4. The Inhibitory Effect of Diadonium on Cholinesterases

Source of Enzyme	Substrate	Substrate Concentration (M)	IC50[†] (M)	IC90[†]
Human plasma	BuCh*	2×10^{-2}	1.2×10^{-4}	1.1×10^{-3}
Human red cell	MeCh	3×10^{-3}	3.7×10^{-5}	2.4×10^{-4}
Rat diaphragm	ACh	3×10^{-3}	5.3×10^{-5}	2.8×10^{-4}
Guinea pig diaphragm	ACh	3×10^{-3}	5.6×10^{-5}	7.6×10^{-4}

*BuCh is a specific substrate of BuChE. It is not hydrolyzed by AChE. MeCh is a specific substrate of AChE. It is not hydrolyzed by BuChE. ACh is hydrolyzed by both BuChE and AChE. Human red cell contains only AChE and human plasma only BuChE. Mammalian muscle contains mostly AChE and a small amount of BuChE (29).

†IC50 and IC90 are the inhibitor concentrations which inhibit the hydrolysis by 50 or 90% (to 50% or 10% of the uninhibited rate). All values are means of 3 experiments.

ence of stimulation rate on the intensity of the block, however, could be antagonized by 4AP.

The inability of neostigmine to antagonize the NM effect of diadonium in rats or mice indicates that it is unlikely that the block is caused by competitive inhibition of the interaction of ACh released by the nerve impulse with the cholinoceptors of the p.j.m.

Theoretically it is conceivable that neostigmine may not antagonize the diadonium block because the concentration of diadonium that causes profound NM block completely inhibits rat muscle AChE. This mechanism has been suggested for the explanation of the inability of neostigmine to antagonize the benzo-quinonium induced NM block in humans (14,15). In rats, however, the NM IC90 of diadonium (6.2×10^{-5} M) only causes about a 50% inhibition of rat muscle AChE. Consequently, if the "cholinesterase inhibition theory" were valid, 0.75×10^{-6} M neostigmine, the concentration that completely inhibits rat muscle AChE, should cause at least partial antagonism of the diadonium block. An added argument against this hypothesis is that, although the inhibitory effect of diadonium on rat and guinea pig muscle AChE are very similar (Table 4), in guinea pigs the NM effects of diadonium were antagonized by neostigmine.

Other possible mechanisms of the diadonium-induced NM block in rats include inhibition of: a) the synthesis of ACh by cholineacetyltransferase (EC 2·3·1·6) (16); b) the uptake of choline into the motor nerve terminal (17); c) loading of the synaptic vesicles with ACh (18,19); d) mobilization of ACh from reserve sites to release sites (3); e) inhibition of release of ACh (20); and f) by obstruction of the ionophores of the p.j.m. (21). Of these possibilities a), b), and c) can be excluded since the NM block caused by these mechanisms is extremely slow in onset and cannot be antagonized by 4AP (unpublished observations 1988). In contrast, the diadonium induced NM block has a rapid onset of action (Fig. 3) and it can be antagonized by 4AP (Fig. 2). The possibility of f) may be eliminated because the NM block caused by block-
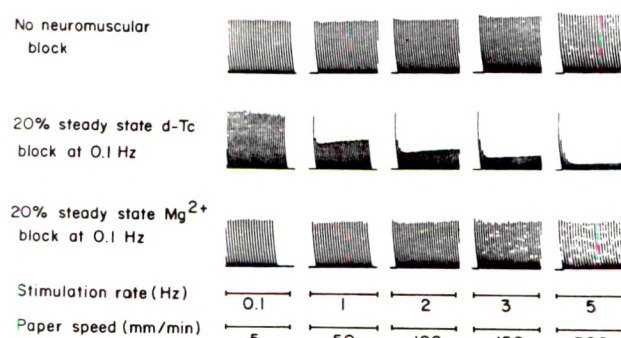
Figure 5. The effect of increasing stimulation rates on the force of contraction (P) of the phrenic nerve—hemidiaphragm preparation of rat. Note that in the control preparation and in the presence of 20% block caused by Mg^{2+}, that inhibits evoked release of ACh, increasing stimulation rates do not diminish P. In contrast in the presence of 20% block by d-Tc, that inhibits mobilization of vesicular ACh, increasing stimulation rates, decrease P.

age of the ionophores (e.g., with 5xIC90 of d-Tc) cannot be reversed by 4AP (unpublished observations 1988), whereas the diadonium block can be rapidly reversed by 4AP (Fig. 2). Of the remaining two possibilities, namely inhibition of mobilization (c) or release (d) of ACh, the latter can be excluded for the reason that, as with diadonium, increasing the rate of stimulation increases the intensity of the partial NM block caused by compounds that inhibit mobilization of ACh (Fig. 3–5) (22). In contrast, the intensity of the partial NM block caused by compounds such as Mg^{++} which inhibit release of ACh is not augmented by increasing stimulation rates (Fig. 5). Therefore, it may be concluded that in rats diadonium blocks NM transmission presynaptically, by inhibiting mobilization of ACh from reserve stores to release sites.

Similar species variation was observed in the NM potency and reversibility of diadonium in anesthetized cats and monkeys (Agoston S, Department of Anesthesiology, University of Groningen Medical School, personal communication). In cats the NM potency of diadonium is relatively high (ED90 = 0.35

mg/kg) and its NM effect can be reversed by neostigmine. In monkeys the NM potency of diadonium is low (ED90 = 5 mg/kg) and its NM effect cannot be antagonized by neostigmine, but can be reversed by 4AP.

The question may be raised why, despite the different primary mechanism of the NM effect of diadonium in rats and mice on one hand, and in guinea pigs on the other hand, in the presence of 20% NM block increasing stimulation rates have similar effect on the intensity of the diadonium block. The answer to this question is that in guinea pigs, diadonium, like d-Tc, blocks NM transmission both pre- (3) and postsynaptically. In the presence of 20% nondepolarization block more than 75% of the cholinoceptors are occupied by the MR molecules (23) and only 25% or less of the cholinoceptors of the p.j.m. are free to interact with ACh released by the nerve impulse. Under these conditions even a moderate decrease of the mobilization rate of ACh to release sites will significantly reduce the statistical probability of interaction between ACh and cholinoceptors. Since mobilization of vesicular ACh is time dependent (22), with increasing stimulation rates, the time available for the mobilization of ACh between stimuli decreases, and the amount of ACh released by each nerve impulse is also diminished. Consequently, the probability of interaction between the decreased amount of ACh and the reduced number of free cholinoceptors is also diminished, and thereby the intensity of the NM block increases. In contrast, in rats and mice, in the presence of NM blocking doses of diadonium, all the cholinoceptors are free to interact with ACh, and in all probability, the cause of the diadonium block is the inhibition of mobilization of ACh. These circumstances also explain the antagonist effect of neostigmine on the progressive intensity of the NM block caused by increasing stimulation rates in some (e.g., guinea pig) but not in other (e.g., rat, mouse) species. In those species where the NM effect of diadonium is primarily postsynaptic, and the mobilization of ACh is decreased only moderately, inhibition of the hydrolysis of ACh by neostigmine will allow the competitive displacement of the diadonium molecules from the cholinoceptors, and allow re-establishment of NM transmission. In those species where the diadonium block is caused primarily by inhibition of the mobilization of ACh, neostigmine is ineffective.

The observation that the potency of diadonium is greater and the NM block is more difficult to antagonize when the preparations are stimulated by short trains of 50 Hz tetani, instead of single impulses at 0.1 Hz, is not unexpected. Similar observations have been made earlier with other nondepolarizing MR

and aminoglycosides (23). The explanation of this finding is that the number of pre- and postsynaptic receptors occupied in the presence of the same concentration of a NM blocking agent is independent from the stimulation rate. With increasing stimulation rates, however, the time available for the mobilization of vesicular ACh is diminished and therefore the amount of ACh available for release by a nerve impulse is decreased. Because of this the statistical probability of interaction between ACh and the free, unoccupied cholinoceptors is much less at fast than at slow stimulation rates. This decreases the depolarization of the p.j.m. and the voltage of the endplate and action potential, and ultimately the force of contraction of the muscle.

In conclusion, the findings presented indicate the site and mechanism of the NM blocking effect of diadonium is postsynaptic in guinea pigs and presynaptic in rats and mice. These differences are probably caused by variation in the affinity of diadonium for ACh recognition sites of the cholinergic receptors of the p.j.m. in these 3 species. In guinea pigs where it is high, low concentrations of diadonium cause postjunctional NM block. In rats and mice where it is low, high concentrations of diadonium interact with nicotinic receptors of the motor nerve terminal, inhibit mobilization of vesicular ACh to its release sites, and thereby cause presynaptic block of NM transmission.

It has been recognized for a long time that there is considerable, quantitative species variation in the NM blocking effect MR (25,26). Furthermore, the relative NM potency of the same MR may change in the opposite direction in different species (25). Thus, for example, pancuronium or vecuronium are about 5 times more potent than d-Tc in humans (26), but about 5 times less potent than d-Tc in rats (28). No differences have been demonstrated, however, in the site(s) and mechanism(s) of any nondepolarizing MR. Search through literature indicates that diadonium is the first bisquaternary NM blocking agent shown to inhibit NM transmission entirely presynaptically in some (e.g., guinea pig, cat, rabbit) and mostly postsynaptically in other mammalian species (e.g., rat, mouse, monkey, human).

The findings presented reinforce the concept that information obtained from pharmacological experiments with MR on subhuman mammalian species may have limited relevance not only to the potency, but also to the site(s) and mechanism(s) of any NM blocking agent. It is therefore necessary to investigate the NM effect and reversibility of any new MR, by accepted pharmacological techniques, in human subjects before their introduction into clinical practice.

References

1. Kharkevich DA. Adamantyl compounds. In: Kharkevich DA, ed. Handbook of Experimental Pharmacology. Vol 79. Berlin-Heidelberg-New York-Tokyo: Springer-Verlag, 1986:473–8.

2. Bunatian AA. Neuromuscular blocking agents of different chemical structure. In: Kharkevich DA, ed. Handbook of Experimental Pharmacology. Vol 79. Berlin-Heidelberg-New York-Tokyo: Springer-Verlag, 1986:567–73.

3. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–43.

4. Matsuo S, Rao DBS, Chaudhry I, Foldes FF. Interaction of muscle relaxants and local anesthetics at the neuromuscular junction. Anesth Analg 1978;57:580–7.

5. Burkett L, Bikhazi GB, Thomas KC Jr, Rosenthal DA, Wirta MG, Foldes FF. Mutual potentiation of the neuromuscular effects of antibiotics and relaxants. Anesth Analg 1979;58:107–15.

6. Foldes FF. 4-Aminopyridin ein neuer Antagonist der neuromuskulären blockage. In: Buzello W, ed. Muskelrelaxantien. Neuere Konzepte ihrer Pharmakologie und klinischen Anwendung. Verlag-Stuttgart-New York: Georg Thieme, 1981:211–8.

7. Hutter OF, Kostial K. Effect of magnesium and calcium ions on the release of acetylcholine. J Physiol (Lond) 1954;12:234–41.

8. Bikhazi GB, Barakat T, Chaudhry IA, Flores CA, Foldes FF. The in vitro interaction of Mg^{2+} with nondepolarizing muscle relaxants. Anesthesiology 1986;65:A118.

9. Foldes FF. The significance of physiological $[Ca^{2+}]$ and $[Mg^{2+}]$ for in vitro experiments on synaptic transmission. Life Sciences 1981;28:1585–90.

10. Smith JC, Cavallito CJ, Foldes FF. Choline acetyltransferase inhibitors: a group of styrylpyridine analogs. Biochem Pharmacol 1967;16:2438.

11. Foldes FF, Smith JC. The interaction of human cholinesterases with anticholinesterases used in the therapy of myasthenia gravis. Ann NY Acad Sci 1966;135:287.

12. Winer BJ. Statistical Principles of Experimental Design. New York, San Francisco, Toronto, London: McGraw-Hill, 1962:83–104.

13. Briscoe G. Changes in muscle contraction curves produced by drugs of the eserine and curarine groups. J Physiol (Lond) 1938;93:194–205.

14. Gordon J. A new relaxing agent: win 2747: a clinical evaluation. Anesthesiology 1953;14:73–6.

15. Hunter AR. The anticurare agents. Br M J 1953;1:640–2.

16. Hemsworth BA, Foldes FF. Preliminary pharmacological screening of styrylpyridine choline acetyltransferase inhibitors. Europ J Pharmacol 1970;11:187–94.

17. Scheuler FW. The mechanism of action of the hemicholiniums. Int Rev Neurobiol 1960;2:77–97.

18. Marshall IG. Studies on the blocking action of 2-(4-phenylpiperidino)-cyclohexanol (AH5183). Br J Pharmacol 1970;38:503–16.

19. Whitton PS, Marshall IG, Parsons SM. Reduction of quantal size by vesamicol (AH5183), an inhibitor of vesicular acetylcholine storage. Brain Research 1986;385:189–92.

20. Del Castillo J, Katz B. Changes in end-plate activity produced by presynaptic polarization. J Physiol (Lond) 1954;124:586–604.

21. Standaert FG. Pharmacology of the neuromuscular junction, The Neuromuscular Junction. Edited by Brumback RA, Gerst JW, New York, Futura, 1984, pp 121–202.

22. Foldes FF, Chaudhry IA, Kinjo M, Nagashima H. Depletion of the readily releasable acetylcholine stores: the weak link in neuromuscular transmission. Anesthesiology 1987;67:A338.

23. Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. J Physiol (Lond) 1967;191:59–90.

24. Foldes FF, Chaudhry I, Ohta Y, Amaki Y, Nagashima H, Duncalf D. The influence of stimulation parameters on the potency and reversibility of neuromuscular blocking agents. J Neural Transm 1981;52:227–49.

25. Paton WDM, Zaimis EJ. The methonium compounds. Pharmacol Rev 1952;4:219–53.

26. Hoppe JO. Observations on the potency of neuromuscular blocking agents with particular reference to succinylcholine. Anesthesiology 1955;16:91–124.

27. Donlon JV Jr, Savarese JJ, Ali HH, Toplik RS. Human dose-response curves for neuromuscular blocking drugs. Anesthesiology 1980;53:161–6.

28. Chaudhry I, Foldes FF. In vitro effect of three new neuromuscular blocking agents. Anesthesiology 1981;55:A220.

29. Smith JC, Foldes VM, Foldes FF. Distribution of cholinesterase in normal human muscle. Can J Biochem Phys 1963;41:1713–20.

Timing of the Anesthetist's Preoperative Outpatient Interview

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Hospitalization arouses anxiety among patients admitted for day bed surgery. The effect of the anesthetist's routine preoperative interview on the anxiety levels of 63 unpremedicated women scheduled for elective outpatient therapeutic abortions was examined using the State-Trait Anxiety Inventory. The anesthetist's preoperative interviews were performed at the following times: Group 1, in the outpatient clinic one week before surgery; group 2, in the day bed unit at the time of admission to hospital; group 3, outside the operating room immediately prior to surgery.

State anxiety was measured before and after patients were seen by the anesthetists. In group 1, and in groups 1 and 2, it was readministered outside the operating room immediately before surgery. Baseline anxiety Trait and State scores were not significantly different in the 3 groups (Trait: group 1, 43.3 ± 2.2; group 2, 36.9 ± 2.3; group 3, 38.8 ± 2.2. State: group 1, 50.6 ± 3.5; group 2, 43.0 ± 2.4; group 3, 49.0 ± 3.0). Only in group 3 did the anesthetist's interview significantly reduce patient's anxiety (before visit 49.1 ± 3.0; after visit 46.0 ± 2.8; P < 0.05). A small but statistically significant reduction in State anxiety scores is achieved when patients are seen by the anesthetist immediately prior to surgery.

Key Words: ANESTHESIA—outpatient.

Hospital admission can be anxiety-provoking (1). Excessive preoperative anxiety is not only unpleasant for patients but may also be associated with detrimental physiologic responses including hypertension, tachycardia, and arrhythmia that may persist into the postoperative period (2,3). Previous studies on surgical inpatients have demonstrated that anxiety rises at least one week before hospital admission and returns to normal levels in the postoperative period only after the patient is assured of an uneventful recovery (4–6).

Traditionally, anesthetists have used preoperative anesthetic visits and preoperative medication to allay anxiety. Egbert and co-workers showed that the anesthetist's visit was more effective than pentobarbital premedication in alleviation of preoperative anxiety (7).

Outpatient surgery poses unique challenges. The administration of preoperative anxiolytic medication, for example, is often avoided because of possible adverse effects in the postoperative period (8). The purpose of this study was to determine the level of anxiety in patients scheduled for outpatient surgery and the appropriate timing of the anesthetist's interview with the patient. We chose to evaluate the effectiveness of the anesthetist's preoperative visit undertaken in the outpatient clinic one week before surgery, in the ambulatory care unit (A.C.U.) the day of the surgery, or immediately prior to surgery.

Methods

The study was approved by the Human Subjects Review Committee at the University of Toronto and informed consent was obtained from 63 healthy female patients. All patients were of ASA physical status I or II and scheduled for therapeutic abortions in the first trimester of pregnancy. Patients were excluded if they had a history of psychiatric illness, were receiving psychotropic or anxiolytic medication, or were unable to perform the tests because of difficulty in understanding English.

Before the anesthetist's preoperative interview, a research assistant interviewed patients to obtain demographic data on age, previous hospitalization and surgery, marital status, children, and drug usage. The assistant then administered the State-Trait Anxiety Inventory and Visual Analogue Scale according to the protocol described below.

Table 1. Demographic Data*

	Group 1† (n = 20)		Group 2‡ (n = 23)		Group 3§ (n = 20)	
Age (yrs, mean ± SE)	25.6 ± 1.4		23.8 ± 1.0		25.0 ± 1.9	
	Yes	No	Yes	No	Yes	No
Number of women with living children	10	10	8	15	6	14
Previous hospitalizations	4	16	12	11	6	14
Previous surgery	17	3	17	6	16	4

*No significant difference among the three groups.
†Anesthetist's Preoperative Interview in Clinic.
‡Anesthetist's Preoperative Interview in Day Bed Unit.
§Anesthetist's Preoperative Interview outside O.R.

The State-Trait Anxiety Inventory provides quantification of anxiety and prevents the problems engendered when anxiety is graded by an observer (9,10). It consists of two separate self-reporting scales that measure state and trait anxiety respectively. Each scale is comprised of 20 statements. The respondents must indicate to what degree each statement is applicable to themselves. The Anxiety-State scale inquires about the subject's level of anxiety at the time the test is administered, whereas the Anxiety-Trait scale requires respondents to describe how they generally feel. Previous studies have shown that Anxiety-State scale scores are sensitive to changes in situational stress and that Anxiety-Trait scores reflect relatively stable individual differences in anxiety proneness (11,12).

The anxiety Visual Analogue Scale consists of a 10 cm line. The left end of the line indicates "no anxiety" and the right end "maximum anxiety." The patients were asked to mark this line to indicate the level of their anxiety. The anxiety Visual Analogue Scale is sensitive to changes in mood and has been shown to correlate highly with results of standardized clinical interviews (13).

The anesthetic preoperative visit was standardized and performed by one of two staff anesthetists. It included a brief preoperative history, physical examination of pulmonary and cardiovascular systems, and evaluation of the upper airway. At the end of the visit patients were given the opportunity to voice any specific concerns or ask any further questions.

Patients were randomly divided into 3 groups according to the timing of the anesthetist's visit. In group 1 (N = 20), the anesthetist's visit was performed in the outpatient clinic one week before surgery. In group 2 (N = 23), the anesthetist saw the patients in the ambulatory care unit (A.C.U.) one hour before surgery, while in group 3 (N = 20), the anesthetist's visit occurred outside the operating room immediately before surgery. In all 3 groups,

Anxiety Trait and Anxiety State tests as well as Visual Analogue tests were administered before the anesthetist's interview. The Anxiety-State and Visual Analogue Scales were then re-evaluated following the interview. In addition, in group 1, the Anxiety-State Scale and Visual Analogue Scale were performed one week later on admission to the ambulatory care unit, and in groups 1 and 2 the same tests were readministered in the patient holding area outside the operating room immediately before surgery.

Within each group, comparisons were performed using a two-tailed Student's t-test. Between groups, comparisons were done by analysis of variance. Results of the Visual Analogue Scale were compared with those of the Anxiety-State Scale by means of a correlation coefficient. Statistical significance was assumed at the $P < 0.05$ level.

Results

The results of the demographic data are summarized in Table 1. The three groups (group 1, N = 20; group 2, N = 23; group 3, N = 20) showed no statistically significant differences in age, previous hospitalization, antecedent surgery, or number of patients with children.

There was no significant difference between the three groups in Anxiety-Trait scores, a measurement of baseline anxiety proneness prior to the anesthetist's interview (group 1, 43.3 = 2.2; group 2, 36.9 ± 2.3; group 3, 38.8 ± 2.2). There also was no significant difference in the baseline Anxiety-State score, a measurement of anxiety level before the anesthetist's interview (group 1, 50.6 ± 3.5; group 2, 43.0 ± 2.4; group 3, 49.0 ± 3.0).

The group Anxiety-State scores at each testing period are shown in Figure 1. There was no reduction in anxiety after the anesthetist's visit in group 1, where the anesthetist's interview was held a week
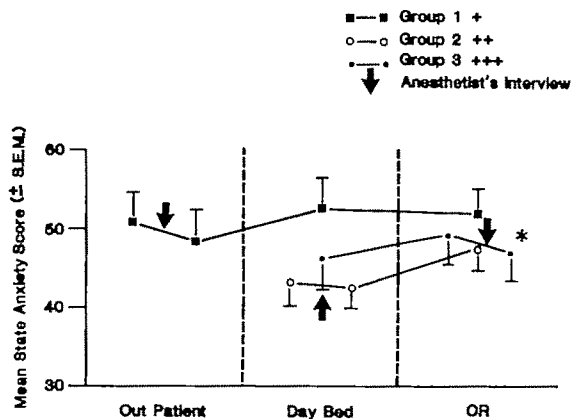
Figure 1. Anxiety-State scores in the three patient groups showing locations of assessment and effect of anesthetist's visit, (Mean ± SEM). + = Anesthetist's Preoperative Interview in Clinic ++ = Anesthetist's Preoperative Interview in Day Bed Unit +++ = Anesthetist's Preoperative Interview outside O.R. *Significant reduction in the State Anxiety Score in group 3 patients; pre vs. post interview score ($P < 0.05$).

beforehand in the outpatient clinic, or in group 2, where the interview was held in the ambulatory care unit. Only in group 3 did the anesthetist's preoperative interview, immediately before surgery, significantly reduce patients' anxiety (before visit, 49.1 ± 3.0; after visit, 46.0 ± 2.8; $P < 0.05$, paired t-test).

However, there was no significant difference in the overall change in anxiety level among the three groups from the time the first State Anxiety scale was applied in each group to the time it was applied immediately outside the operating room. There was no significant difference in the level of anxiety immediately before surgery among the three groups (group 1, 52.4 ± 3.0; group 2, 47.7 ± 2.1; group 3, 46.95 ± 2.8).

The anxiety score measured by Visual Analogue Scale was significantly correlated with the Anxiety-State scores (R = 0.68).

Discussion

It is difficult to compare the results of our study with previous studies of perioperative anxiety because of variations in the methods used to measure anxiety and differences in the populations studied. Egbert and co-workers studied anxiety in inpatients, both male and female, prior to elective surgery (7). They concluded that the anesthetic visit was more effective than pentobarbital in reducing anxiety. In their study no objective measurement of anxiety was made.

Leigh and co-workers (14) used State-Trait Anxiety Inventory to quantify the effect of the anesthetic visit

on anxiety amongst inpatients. They found a statistically significant reduction in Anxiety-State scores when their patients were seen preoperatively by the anesthetist. In their study, mean pre-visit scores were 46.5 ± 7.5, whereas scores after the interview were reduced to 32.8 ± 4.3. The latter scores are compatible with low to normal stress levels.

Our patients had high Anxiety-State scores one week prior to the proposed outpatient surgery. Anxiety-State scores were also elevated when measured the morning of the proposed surgery on admission to the hospital with the patient immediately outside the operating room. These elevated Anxiety-State scores are similar to results obtained in other preoperative inpatient populations (5,6,14).

In addition, we showed the anesthetist's preoperative interview immediately before surgery to be effective in reducing anxiety. Anxiety scores before and after the interviews were not significantly different in the group of patients seen by the anesthetist in the outpatient clinic or in the ambulatory care unit. Only in the group seen by the anesthetist immediately outside the operating room was there a significant reduction in anxiety scores. Even in this group, however, scores after the interview were still in the range associated with stress. Our results are contrary to Leigh and co-workers who found that the anesthetist's preoperative visit was able to abolish anxiety (14).

Several factors may explain the discrepancy between the findings of Leigh et al. (14) and our results. First, the populations studied are not comparable. Leigh et al. study included both males and females whose ages ranged from 20 to 60 years, whereas our study was confined to young females. Secondly, Leigh and co-workers did not specify the surgical procedures undertaken; our study was restricted to outpatient uterine suction dilatation and curettage. Many patients in our study felt ambivalent about the surgery. Some patients underwent surgery without the knowledge and support of family members. When patients were seen in the outpatient clinic, they were still not assured of acceptance for therapeutic abortion by a review committee. These factors might have accounted for the increased level of anxiety at that time.

Not all anxiety may be attributable to anesthesia. Norris and Baird studied 500 patients preoperatively to determine the incidence and etiology of patient anxiety. Sixty per cent of their patients were found to be anxious, but only 7% felt that their anxiety was related to anesthesia (15). Other researchers have suggested that the anesthetist's preoperative visit does not predictably alleviate anxiety. Collins and

Moore (16) were unable to demonstrate any difference in anesthetic requirements during diagnostic dilatation and curettage between a group prepared with a preanesthetic interview and a control group that received no visit. Williams et al. (17) demonstrated a paradoxical increase in anxiety in relatively non-anxious patients seen pre-operatively by the anesthetist.

It appears that the cause of patient anxiety is multifactorial, and that it may change over time. Anesthesia-related fears may increase as the operation draws nearer. This may explain the greater impact of the anesthetist's interview in alleviating anxiety immediately before surgery shown in this study.

In conclusion, we found a high level of anxiety in patients scheduled for suction dilatation and curettage. The anesthetic visit in an outpatient clinic or ambulatory care unit was ineffective in reducing anxiety levels. There was, however, a statistically significant reduction in anxiety in patients seen outside the operating room immediately prior to surgery. The optimal time of the preoperative anesthetic visit to reduce the anxiety of patients awaiting a therapeutic abortion is just before surgery, but even at this time, the level of anxiety in these patients may still be high. Thus, we should reassure our patients immediately before surgery.

References

1. Rockwell DA, Pepitone-Rockwell F. The emotional impact of surgery and the value of informed consent. Med Clin North Am 1979;63:1341–51.
2. Ramsey MAE. A survey of pre-operative fear. Anaesthesia 1972;27:396–402.
3. Williams JGL, Jones JR. Psychophysiological responses to anesthesia and operation. JAMA 1968;203:415–17.
4. Martinez-Urrutia A. Anxiety and pain in surgical patients. J Consulting and Clin Psychol 1975;43:437–42.
5. Spielberger CD, Auerbach SM, Wadsworth AP, Dunn TM, Taulbee ES. Emotional reactions to surgery. J Consulting Clin Psychol 1973;40:33–8.
6. Johnston M. Anxiety in surgical patients. Psychol Med 1980;10: 145–52.
7. Egbert LD, Battit GE, Turndorf N, Beecher HK. The value of the preoperative visit by the anesthetist. JAMA 1963;185:553–5.
8. Korttila K, Linnoila M. Psychomotor skills related to driving after intramuscular administration of diazepam and meperidine. Anesthesiology 1975;42:685–91.
9. Halpern LM. Rational choice of preoperative medication: the emperor's new clothes? Anesthesiology 1977;47:239–40.
10. Norris W. The quantitative assessment of premedication. Br J Anaesth 1969;41:778–83.
11. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory ("Self-Evaluation Questionnaire"). Palo Alto, Consulting Psychologists Press (form Y), 1983.
12. Johnson DT, Spielberger CD. The effects of relaxation training and the passage of time on measures of state and trait anxiety. J Clin Psychol 1968;24:20–3.
13. Aitken RCB. Measurement of feeling using Visual Analogue Scale. Proc Roy Soc Med 1969;62:989–93.
14. Leigh JM, Walker J, Janaganathan P. Effect of preoperative anaesthetic visit on anxiety. Br Med J 1977;2:987–9.
15. Norris W, Baird WLM. Pre-operative anxiety: a study of the incidence and aetiology. Br J Anaesth 1967;39:503–9.
16. Collins NW, Moore RC. The effect of a preanesthetic interview on the operative use of thiopental sodium. Anesth Analg 1970;49:872–6.
17. Williams GL, Jones JR, Workhoven N, Williams B. The psychological control of preoperative anxiety. Psychophysiology 1975;12:50–4.

Special Article

Informed Consent:
A Review

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Key Words: MEDICOLEGAL, informed consent.

Informed Consent

Starting with the basic exposition that ". . . every human being of adult years and sound mind has a right to determine what shall be done with his own body . . ." (1), interpretation of the concept of informed consent has undergone many metamorphoses (2), and continues to generate lively discussion in both the legal and philosophical worlds (3–5). The concept of informed consent is not only open to differing interpretations, but also generates confusion about its legal implications (6,7).

Both legal and moral perspectives ought to be considered when thinking of informed consent. The former emphasizes financial compensation for unfortunate medical outcomes, while the latter concentrates on the autonomous choices of patients and research subjects. Thus, the legal approach focuses on the physician and his or her duty toward the patient, while the moral approach focuses on the patient and his or her right to personal autonomy.

Of how much importance is informed consent, and should anesthesiologists concern themselves with it at all? In terms of the frequency with which it is invoked as a cause of action in medical malpractice litigation, informed consent need not be of major concern. A Health, Education, and Welfare Agency medical malpractice commission found that as of 1971 there had been only 90 American appellate decisions in which consent was a *major* issue (8). Another study undertaken by the National Association of Insurance Commissioners reported that, in a survey of claims resolved over a 12-month period in 1975–76, informed consent was raised as an issue in only 3% of the cases (9). Moreover, even when the issue is raised in litigation, in no reported cases have damages been awarded to a plaintiff solely for dignitary harm in the absence of accompanying injury (9).

While informed consent is not of major significance in medical malpractice litigation, as a concept embodying patient rights it is perceived by many as a distillation of some of the more important ethical values in the health-care setting. In the late 1970's, President Carter commissioned a study on ethical problems in medicine and related research. The Commission held the issue of decision making so important that it devoted three books to its examination (10).

The philosophical foundations of the informed consent doctrine will now be briefly examined, followed by a history and analysis of its jurisprudential aspects.

Philosophical Foundations

Any relationship between physician and patient must include an understanding as to how medical-treatment decisions will be made. Some observers feel that physicians have assumed an Aesculapian authority over their patients (5). A feeling of powerlessness in the face of disease and intimidation by modern medical technology have led many patients to accept this view of their physician, thus perpetuating an authoritarian and essentially unequal relationship in the decision-making process.

From a philosophical perspective, informed consent doctrine emphasizes equalization of the physician/patient relationship and decision-making rights. Respect for patient autonomy forms the basis of modern informed consent doctrine, while the concepts of beneficence and justice complete the moral triad.

Autonomy

The term "autonomy" is derived from the Greek "autos" meaning self, and "nomos" meaning rule of law. These two words were combined to refer to political self-governance in the ancient city-state. In modern philosophical terms, the term autonomy has come to refer to self-governance through adequate understanding.

It is insufficient merely to allow the patient final say in deciding a treatment alternative, without first providing him or her with the relevant medical information. This information must include the risks, benefits, and alternatives to the proposed treatment. Allowing the patient final say in the decision without providing sufficient information would be an example of consent without the "informed" part of the formula.

Providing the patient with all the information but then denying him or her the right to make a decision, would vitiate the other end of the equation, thereby also vitiating the patient's autonomy.

The concept of autonomy therefore embraces the right both to receive information *and* the right to act on it by giving or withholding consent. The amount and nature of information to be provided to the patient are controversial and depend, inter alia, on what information is available, the nature and importance of that information, and certain patient variables. This will be discussed in the legal section.

Beneficence

The welfare of the patient is the goal of health care. Historically this goal has been expressed by the maxim "primum non nocere", "in the first place, do no harm." However, recent scholarship has shown that the more precise formulation of this primary moral injunction is "help, or at least do no harm" (11). This formulation envisions the obligation of physicians to provide a benefit to patients, not merely to avoid harm.

How are medical professionals to provide benefit to patients within the decision-making process? Clearly, benefit accrues by providing the patient with sufficient information with which to arrive at an informed decision, and subsequently by allowing that patient to make decisions relating to his or her own health care. The concept of beneficence embraces the *process* of consent, not the actual decision reached by the patient. Providing the patient with both the opportunity and the information to exercise his or her right to self-determination, fulfills the benefit (beneficence) part of the equation. Benefit is derived, in philosophical terms, regardless of the reasonableness or otherwise of the decision reached by the patient. Affording

the patient the opportunity to make decisions is determinative, not the actual decision reached.

Justice

Simply stated, justice is served when people or groups of people are treated equally under essentially similar circumstances. As a philosophical concept, justice has broad implications in politics, civil rights, and criminal justice. While of some importance doctrinally in the consent area, it is not of major significance, and is mentioned here for the sake of completeness only.

Legal Foundations

Traditionally, many cultures, including our own, have invested healers a unique deference and authority in their relationships with their patients. Yet, this authority is not without limits (12). Within the Anglo-American legal tradition, it has long been recognized that physicians must obtain consent from their patients prior to initiating treatment. The earliest reported case dealing with consent to medical treatment is generally acknowledged to be the 18th-century English case of Slater versus Baker and Stapleton (13), in which the plaintiff hired Drs. Slater and Baker to remove the bandages from a partially healed leg fracture. Instead, the defendants refractured the leg and placed it in an experimental apparatus to stretch and straighten it during the rehealing. The court, in ruling for the plaintiff, stated: ". . . and indeed it is reasonable that a patient should be told what is about to be done to him, that he may take courage and put himself in such a situation as to enable him to undergo the operation" (14).

While the earlier cases generally dealt with lack of any consent at all, the twentieth century has spawned the concept of informed consent, thus expanding, and in some cases complicating, the legal situation doctrinally.

As a starting point it would be useful to review the issue of consent alone first and then discuss *informed* consent.

Consent

Lack of any consent generally gives rise to an action in battery, defined as a tort (civil wrong) resulting from intentional and unpermitted contact with the plaintiff's (patient) person (15). In order to be liable for battery the defendant (physician) must have done some positive and affirmative act, and the act must cause, and must be intended to cause, an unpermitted contact (15). It is not essential that the plaintiff be

conscious of the contact at the time it occurs; personal integrity is protected, even if the patient is asleep or anesthetized (16,17). It matters not whether the intent of the defendant is evil or benign, whether the contact is meant in jest, or even whether the contact results in injury or damage to the plaintiff.

Common parlance frequently combines the term assault with battery (as in assault and battery), but, in fact, assault has a separate and distinct meaning within legal semantics, viz "a threatening approach the puts a person in fear of a battery" (18). It would thus constitute a battery to anesthetize a patient or insert invasive monitoring lines without permission. Any act which violates a patient's personal integrity through physical contact must be consented to. Absence of this consent constitutes a battery.

Consent may be signaled in several ways. It may be expressed, either in writing or verbally. Verbal consent is legally and ethically just as valid as written, except that proof (evidence) of verbal consent may be difficult after the fact. Consent may also be implied, as when a patient acts affirmatively in such a way as to infer that he or she agrees (consents) to the impending procedure (holding out an arm for placement of an intravenous line; not moving while a nerve block is being performed).

The only exception to the above rule (obtaining consent) would be an emergency situation where the patient is incapable of signaling consent or otherwise, and prompt action is needed to save life.

Informed Consent

The above section dealt with situations in which no consent at all is obtained. There are few problems doctrinally with the concept of battery. Just the opposite is true, however, with informed consent. The term "informed" deals with explanation of the proposed procedure or anesthetic or intervention beyond the mere performance of the procedure or anesthetic itself. In very general terms, "informed" refers to explanation of the risks, benefits, and alternatives of the proposed procedure or anesthetic. While seemingly simple, the phrase "risks, benefits, and alternatives" has spawned vigorous debate regarding the depth and extent of these disclosures.

In 1918, the court spoke of a doctor's duty to warn a patient of the possible adverse consequences of using a remedy (19). This was one of the first examples of consent requirement going beyond mere description of the proposed intervention.

In the latter part of this century, the nature and quality of information provided to the patient assumed importance judicially. The phrase "informed

consent" was first articulated in a 1957 decision, Salgo versus Leland Stanford, Jr., University Board of Trustees (20). In this case, the plaintiff suffered permanent paralysis as the result of a translumbar aortography, and sued his physicians both for negligence in their performance and in failing to warn him of the risk of paralysis. The court found that physicians had the duty to disclose "any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment" (21).

Thus, since 1957 there exists an added element in the consent doctrine. Lack of any consent at all can provide the basis for a suit in battery. Inadequate explanation, as part of the consent process, of the risks, benefits and alternatives to the proposed procedure or treatment will now lay the practitioner liable to an action based on negligence. The term negligence relates to the negligent omission of full disclosure.

The issue today is thus reduced to the amount and quality of disclosure, a difficult task indeed. A brief look at the judicial history of quality and quantity of information to be disclosed to the patient might clarify the issue, although it must be emphasized that there exist no simple formulae to help in the decision. Central to the question of quantity and quality of information provided the patient is the issue of standards, and by whom they should be set. Should it be the patient, who, with brilliant hindsight would exclaim in court that he or she would never have undergone the procedure had he known of the risks; or the physician who might be more guided by paternalism or economic self-interest in underdisclosing risks and thus encouraging the patient to undergo the proposed procedure?

The Professional Standard Rule

Initially, the courts relied on the judgment of the physician in defining disclosure standards. A 1960 landmark Kansas case states well the philosophy linking the disclosure obligation to the standard practice of responsible physicians in same or similar situations: "The duty of the physician to disclose . . . is limited to those disclosures which a reasonable practitioner would make under same or similar circumstances. How the physician may best discharge his obligation to the patient . . . involves primarily a question of medical judgment. [t]he physician's choice of plausible courses should not be called into question if it appears . . . that the physician was motivated only by the patients best therapeutic interests . . ." (22).

The policy underlying the rule was consistent with

the high esteem in which physicians were generally held and, perhaps more important to judicial decisions, was consistent with the way other medical malpractice decisions are made, namely through defining standards of care extant in the medical fraternity.

The Lay Standard Rule

The above standard of disclosure, the professional standard, did not last forever. A new rule on measurement of standards of disclosure emerged in 1972 with the case of Canterbury versus Spence (23). The plaintiff in this case underwent a cervical laminectomy, following which he became quadriplegic. In suing his surgeon, he did not allege negligence in the performance of the operation itself, but rather claimed that he was negligently misinformed about the risk of serious neurologic sequelae following that kind of surgery. In holding for the plaintiff the court ignored the prevailing standard of disclosure (namely, that neurosurgeons generally did not apprise their patients of that particular risk as it was of low incidence) and fashioned a new rule, based on patient needs. The court went on to hold that the physician is required to disclose information to patients unless, in the judgement of the physician, due care required some degree of non-disclosure under the circumstances (the so-called therapeutic privilege). The extent of disclosure otherwise required was to be measured exclusively by a ". . . reasonable standard of what is material to the patient's decision rather than a professional standard based on customary practice" (23).

This new rule focused on the so-called "new consumerism" in health care, an extension of the patient's right to self-determination, where the patient is viewed as consumer of health care, the physician as provider.

While intuitively appealing, the above helps us little in defining what is either "reasonable" or "material." What might seem reasonable or material to the patient at trial could obviously be the product of self-interested hindsight, thus exposing every consent process to potential later litigation. This problem was recognized by the Canterbury court, which went on to say that requiring physicians to divulge *all* risks would "summon the physician to second-guess the patient, whose ideas on materiality could hardly be known to the physician." Instead, "on the basis of his medical training and experience the physician can sense how the average, reasonable patient expectedly would react" (25).

Waltz and Scheuneman defined material risk as follows: "A risk is material when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk in deciding whether or not to forgo the proposed therapy" (26). Under the new theory, the patient must prove that disclosure of the risk would have caused the patient to forgo the therapy, and thus the non-disclosure of the risk "caused" the injury that resulted when the risk materialized.

In summary, the Canterbury court reaffirmed in 1972 that self-determination is the sole justification and goal of informed consent, and that the patient's needs for information rather than the physician's practices must form the basis of any adequate standard of disclosure.

But while the Canterbury decision appeared to signal a bold and significant change in emphasis in consent law, the professional practice standard was not completely displaced in American informed consent law (26).

A number of state legislatures have incorporated the professional custom standard in legislation, usually at the urging of state and local medical societies (9), so that today, while the patient-based materiality standard of Canterbury carries some weight, it probably represents a minority position legally.

Informed Consent Status Today

Decision making in the health-care setting has undergone considerable change this century. Early case law focused solely on lack of consent, while the past thirty years have witnessed the development of standards of disclosure extending beyond mere description of the proposed intervention. There is little disagreement today that physicians owe a duty to their patients to disclose the proposed procedure and the risks, benefits, and alternatives appurtenant thereto.

How far the disclosures muse extend remains controversial, both in an ethical and a legal sense. Which of the disclosure standards will emerge as the dominant legal doctrine, and how terms such as materiality and reasonableness are defined will surely provide grist for legal and ethical debate in the future, as in the past.

In the field of anesthesiology, a field fraught with risk, time should be spent with the patient prior to surgery. Risks and alternative anesthetic modalities should be openly discussed. Undoubtedly, deciding which risks to disclose is a difficult issue. Variables in patient age, concurrent illness, and the nature of the proposed surgery make it impossible to provide

"cookbook" recommendations. It would not be un-reasonable to mention all material risks, i.e., those risks which the average, "reasonable" patient would regard as significant. One court has defined "material" in the following way: "Materiality is, in essence, the product of risk and its chance of occurring" (27). Thus risk of a minor injury (such as a minor abrasion on the lip from intubation) with a high probability of occurrence probably need not be mentioned, whereas a more serious injury (such as death in an ASA physical status 4 patient), while less common, would be worthy of mention by virtue of its gravity.

A question frequently asked is whether the risk of death should routinely be mentioned. As indicated above, in most patients this particular risk would not be thought of as material. While of an extremely serious nature, the probability of death in otherwise healthy patients undergoing routine surgery is remote, thus tipping the severity-frequency product out of the bounds of materiality.

As mentioned in the introduction, issues of informed consent standing alone rarely arise in medical malpractice litigation. There are two significant reasons for this. First, most patients become plaintiffs only when they suffer injury, and most of the time these injuries are the result of negligence. Regular medical negligence is easier to prove than failure to obtain consent, and plaintiffs will usually assert negligence, rather than pursue the more tenuous legal doctrine of lack of informed consent. Second, for lack of consent to be actionable, the patient has to prove not only that he or she would have forgone the anesthetic or procedure but also that the risk in fact materialized. A charge of non-disclosure alone, without injury, gives rise to a so-called dignitary tort, for which the courts rarely, if ever, provide compensation.

Summary

Of paramount importance is the respect for autonomy and right to self-determination inherent in an ethically sound decision-making process. The President's Commission clearly summarized the prevailing view of informed consent when it stated: "ethically valid consent is a process of shared decision making based on mutual respect and participation, not a ritual to be equated with reciting the content of a form that details the risks of a particular treatment or intervention" (9).

References

1. Schloendorff versus Society of New York Hosp., 211 N.Y. 125, 105 N.E. 92, 95 (1914).

2. Annotation, 56 A.L.R. 2d 695, 704–7, 716–17 (1957).

3. Gibbs RL. The evolving concept of informed consent. Legal Perspectives in Anesthesia. Sept/Oct 1985:1–4.

4. Schwartz R, Grubb A. "Why Britain can't afford informed consent." Hasting's Centre Report 1985;15(4):19–25.

5. Katz J. The silent world of doctor and patient. The Free Press, 1984.

6. Furrow BR. Informed consent: a thorn in medicine's side? an arrow in laws quiver? Law, Medicine and Health Care 1984; 12(6):268–73.

7. Rozofsky FA. Consent to treatment; a practical guide. Boston: Little, Brown & Co., 1984.

8. Law S, Polan S. Pain and Profit: The politics of malpractice. Harper and Row, 1978:112–3.

9. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Making health care decisions. U.S. Government Printing Office. 1982: 21,23,2.

10. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. U.S. Government Printing Office. 1982: Vol. 1–3.

11. Jones WHS. Epidemics (Hippocrates). Massachusetts: Harvard University Press, 1923:23.

12. McCullough LB. Historical perspectives on the ethical dimensions of the patient physician relationship: the medical ethics of Dr. John Gregory. Ethics in Science and Medicine 1978;5:47–53.

13. 95 Eng. Rep. 860 (K.G. 1767).

14. 2 Wils. K.B. 362.

15. Prosser WL. Law of Torts. 4th ed. Minnesota: West Publ. Co., 1982:35,43.

16. Mohr versus Williams, 1905, 95 Minn. 261, 104 N.W. 12.

17. Hively versus Higgs, 1927, 120 Or. 588,253, p.363.

18. Rosoff AJ. Informed consent: a guide for health care providers. Maryland: Aspen Publications, 1981:3.

19. Hunter versus Burroughs, 123 Va. 113, 96 S.E. 360 (1918).

20. 154 Cal. App. 2d 560, 317 p.2d 170 (1957).

21. Salgo versus Leland Stanford Jr., Univ. Board of Trustees, 317 p.2d 170, 181 (1957).

22. Natanson versus Kline, 186 Kan. 393,409–410, 350 p.2d 1093, rehearing denied, Kan. 186,354 p.2d 670 (1960).

23. Cantebury versus Spence, 464 F.2d 783,784 (D.C. Circuit 1972).

24. Faden RR, Beauchamp TL. A history and theory of informed consent. New York: Oxford University Press, 1986:123,5,6.

25. 464 F. 2d 787

26. Waltz JR, Scheunemann T. Informed consent and therapy. Northwestern University Law Review 1970;64:628.

27. Winkjer versus Herr, 22 N.W. 2d 579,588 N.D. (1979).

Review Article

Regional Anesthesia in Children

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The practice of pediatric regional anesthesia is several milleniums old. An Egyptian low relief of Saqqarah, carved about 2500 BC, shows a scene of circumcision (Fig. 1) in which an object (perhaps the famous "Stone of Memphis") appears to be employed for inducing anesthesia of the penis before the operation. The later occidental civilizations turned away from these traditional analgesic practices until the end of the nineteenth and the beginning of the twentieth centuries (1–6). During a brief period, spinal, then supraclavicular and caudal blocks gained enthusiastic but transient acceptance. However, these techniques fell progressively into disuse and were almost lost by the end of the first half of the twentieth century.

The reasons for such disinterest were numerous. Some pertained to the considerable improvements in general anesthesia, both technically, due to the widespread acceptance and use of tracheal intubation and mechanical ventilation, and pharmacologically, due to the availability of safer agents (especially halothane). In contrast, regional anesthetic agents and techniques remained almost unchanged, and little information was available on the pharmacology of local anesthetics in children. Compared to general anesthesia, regional anesthesia was time-consuming, less reliable and potentially hazardous (with risks of legal complications), variable in duration and not flexible (lightening or deepening the level of anesthesia is impossible). Pediatric regional anesthesia required special skills and specially designed re-usable

pediatric devices, the sterilization of which was often difficult. Furthermore, most surgeons preferred that patients be immobilized and unconscious.

In the early 1970s however, papers on pediatric regional procedures began to appear in the medical literature (7–10). Since then, growing attention has been paid to regional techniques, especially with increased acceptance of the concept that general and regional anesthesia could be complementary. Safer local agents are now available and the pharmacological effects of most local anesthetics are now well documented, even in neonates. Several technical difficulties have also been overcome not only with the more general application of nerve stimulators for precise localization of peripheral nerves but also the availability of regional anesthesia equipment specifically designed for use in children. The almost complete absence of hemodynamic effects of regional (including spinal and epidural) anesthesia in infants and young children, together with realization that anesthesiology includes treatment of all forms of pain in all patients have led to renewed interest in pediatric regional anesthesia.

General Considerations

Specificity of the Pediatric Period

Developmental and anatomical state. Embryological processes are incomplete at birth. Myelinization of nerve fibers begins during the fetal period in cervical spinal segments, and extends caudad (11–13). Ventral roots are myelinized prior to dorsal roots, and the myelination process of nerve trunks, especially in the lower extremities, is not achieved until the end of the second year of life. Since the myelin sheath is a lipid layer, the degree of myelination of nerve fibers influences considerably the pharmacodynamic effects of local anesthetics (which are, of course, lipid soluble) (14).

Figure 1. "Penile block" prior to circumcision in Ancient Egypt (Saqqarah, approximately 2500 B. C.).

Other important events of the fetal period are the unequal rates of growth of the spinal cord, the dura mater and the spinal canal that cause the end of the spinal cord and the dural sac to lie at progressively higher levels, and the orientation of the last spinal roots to be modified (15,16). At birth, the dural sac ends at S3–S4 levels; the adult level (S2) at which the dura ends is not reached before the second year of life.

Ossification of vertebrae is still in progress at birth and remains so throughout childhood. The two halves of the vertebral arches join together posteriorly during the first year of life, while their junction with the vertebral body is ossified between the third and sixth year of life. The transverse and spinous processes, and the upper and lower surfaces of vertebral bodies remain cartilaginous until puberty. The ossification of the sacrum is only achieved after the 25th year. Thus, the sacrum, cartilaginous in children, may be easily traversed by sharp needles during inappropriate block procedures. In addition, the dorsal aspect of the sacrum is almost flat in young patients and the sacral hiatus, which is identified by easily palpable sacral cornua, is large. Its location is facilitated by the sharp angle formed by the major axes of the sacrum and the coccyx.

Perineurovascular sheaths are loosely attached to underlying structures in children, thus allowing considerable spread of anesthetic solutions along nerve trunks (Fig. 2A). However, the lower limit of the interscalene space, at the level of the coracoid process (17,18), cannot be changed or increased by injecting a large volume of anesthetic solution even if a tourniquet is placed at the proximal part of the limb and inflated before injection (Fig. 2B). Therefore, axillary approaches cannot result in block of nerves emerging from the brachial plexus above the coracoid process (such as, usually, the musculocutaneous, medial brachial cutaneous and axillary nerves) unless the tip of the needle traverses this lower limit of the interscalene space. However, in this case, the same dangers as following peri-subclavian artery approaches must be expected.

The different sheaths surrounding nerve fibers within nerve trunks differ substantially in their potential for acting as barriers to the spread of local anesthetic solutions. As in adults, the epineurium is usually considered the main obstacle to intraneural diffusion whereas the perineurium does not play a significant role. The structure of the endoneurium varies widely with the age of the patient and the type of nerve: it is loose and represents little barrier to drug diffusion in young patients, but becomes progressively enriched in connective fibers in older patients with a resulting in increase in time of onset of effect but with prolongation of its duration.

The epidural space is multicompartmented posteriorly in children as in adults (19) by a median epidural band, usually termed the plica mediana dorsalis, which is even thicker in children than in adults (Fig. 3), and this may account for unilateral blockade and/or difficulty in introducing a catheter through an epidural needle. The epidural fat is very fluid in infants and becomes more dense (and thus, less permeable to local anesthetics) in children over 7–8 years of age (20,21). As in adults, epidural pressure is subatmospheric. However, since the subcutaneous tissues and vertebral ligaments are less densely packed in infants and young children, the loss of resistance felt as the needle crosses the ligamentum flavum is less marked than in adults.

The subarachnoid space in children is similar to that of adults. The spinal fluid pressure is lower than in adults and varies widely with the position of the patient. In children weighing less than 15 kg, the overall volume of cerebrospinal fluid per kg of body weight (4 ml/kg) is twice that of adults (2 ml/kg) (22); this may account for the significant increase (in terms of mg/kg) in the requirements for local anesthetics during spinal anesthesia in young patients.

Perception and assessment of pain in children. Three

A

B
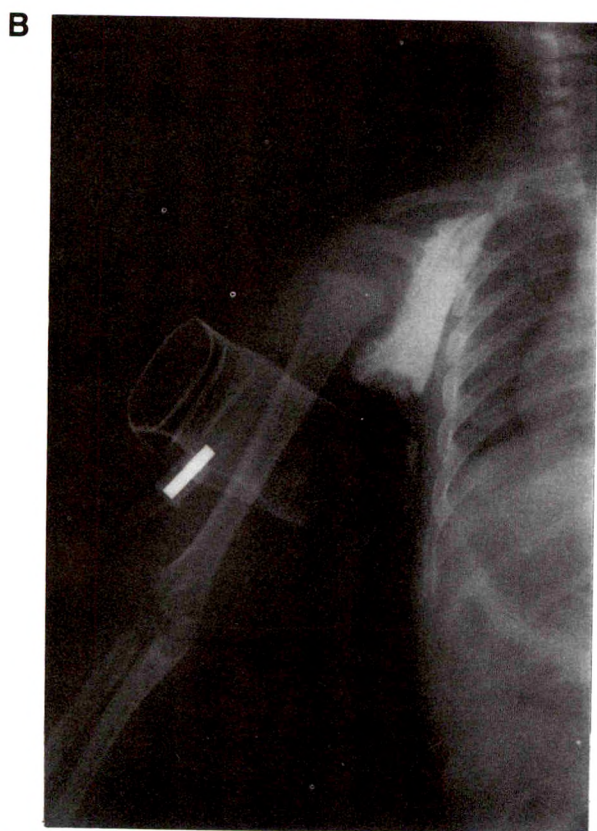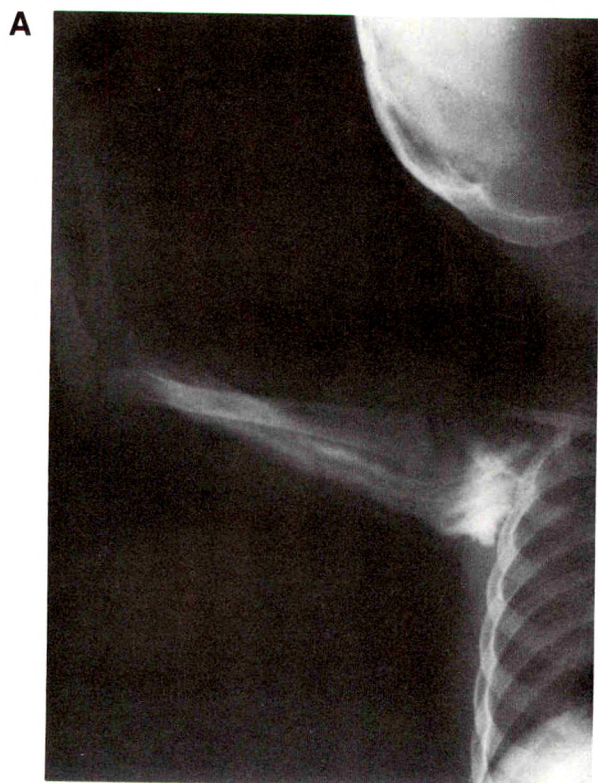
Figure 2. Spread of solutions (1 ml/kg) containing contrast media within perineurovascular spaces. **A.** Axillary perineurovascular space: note the distal spread of the solution, whereas the interscalene space is not reached by the solution. **B.** Injection in the same space after placement of a tourniquet at the root of the upper limb: note that the limit between the interscalene space and the axillary perineurovascular space is not increased by the injected solution.
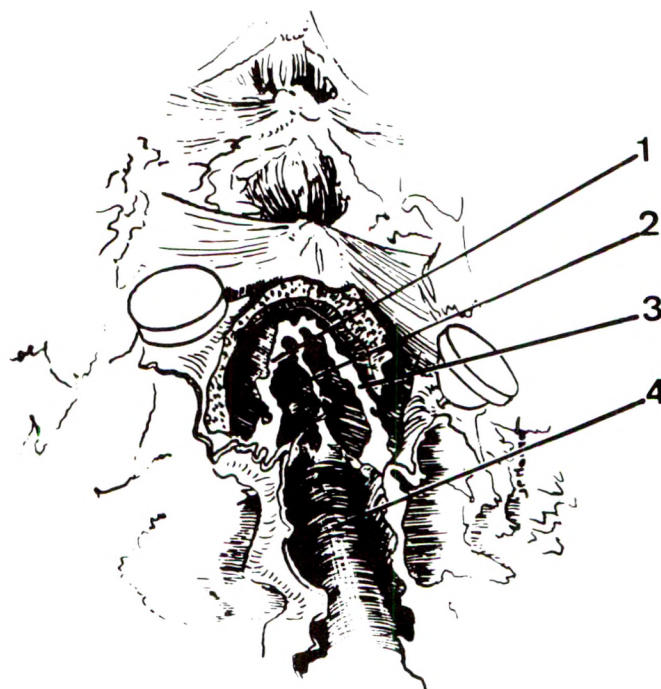
Figure 3. Compartmentation of the posterior part of the epidural space. 1. Right lateral epidural band. 2. Plica mediana dorsalis. 3. Left lateral epidural band. 4. Dura mater.

main components are usually identified in the perception of somatic pain (23): 1) motivational-directive, transmitted by C unmyelinated fibers (slow pain) and leading to protective reflexes (autonomic and motor activities such as contraction of muscles and rigidity); 2) sensory-discriminatory, transmitted by A delta myelinated fibers (fast pain), allowing accurate identification and location of the nociceptive stimulus and eliciting withdrawal reactions; and 3) cognitive-

evaluative, which is multifactorial but mainly a cerebral process and does not result from the stimulation of peripheral receptors.

In neonates, pain is almost exclusively limited to the motivational-directive component. As myelination develops, fast pain becomes more important, while the cognitive-evaluative component develops throughout childhood and adolescence, being influenced by a variety of environmental, educational, social, cultural and individual factors, including previous experiences of pain.

A few years ago, it was commonly believed that neonates did not feel pain, at least at a cortical level. Several studies of pain perception and response have focused on behavioral changes, hormonal responses, autonomic disturbances and analysis of crying behavior (24–26). The results of these studies support the hypothesis that nociceptive stimuli result in significant behavioral and physiological changes in the neonate, and that these changes may persist for several hours, i.e., neonates feel pain. Nevertheless, it is difficult to precisely assess pain in such young patients: cries carry little information about the cry evoking situation and cannot be used to determine whether or not the patient feels pain. However, this "graded signal" and the response to stimulation can be indicative of the level of general comfort of the baby. Comparison with the preoperative neonate's demeanor usually allows an estimation of pain, although it still remains subjective.

In infants, characteristic facial expressions, behavioral changes, sleep and eating disturbances, failure to be consoled by nurses and parents, and/or the occurrence of behavioral regressions are the most usual symptoms indicative of pain. With some experience, these symptoms can be used for assessing pain (but still very subjectively).

Even in toddlers and pre-school age children assessment of pain is difficult. In spite of their developing ability to communicate, these children have little experience with pain perception and little understanding of analog concepts (27–30). Pain is often interpreted as an all-or-none phenomenon. In children aged 1 to 7 years, the best way to assess pain is by using the CHEOPS pain scale (31). After age 7, the psychological component of pain becomes increasingly important.

The assessment of pain in school age children, and especially in adolescents, is progressively easier and increasingly similar to assessment in adults using visual analogue scales and behavioral responses (32,33).

Pharmacological Characteristics

Pharmacokinetics of local anesthetics. After injection into tissues, local anesthetics diffuse towards both their site of action and blood vessels that they enter quite freely. The systemic vascular absorption of local anesthetics correlates positively with 1) the number and size of capillaries at the site of injection; 2) local blood flow (34), a considerably more important factor in infants and children than in adults; and 3) a high blood/tissue partition coefficient of the drug. Addition of epinephrine considerably retards the systemic uptake of local anesthetics, especially when local blood flow is abundant, i.e., in infants.

The blood concentration of local anesthetics follows a time-related profile (35,36). This is usually assessed by measuring the peak drug concentration (C_m), the time necessary for reaching the C_m (T_{peak}) and for eliminating half the given dose ($T_{\frac{1}{2}beta}$) (Table 1) (37–42). After systemic uptake, the local anesthetic is redistributed to different body fluid compartments and tissues and progressively eliminated by plasma or hepatic metabolism; only small amounts of local anesthetics are excreted in unchanged form in urine (and gastric juice, especially in neonates).

Overall drug distribution is assessed by measuring the steady state volume of distribution (V_{DSS}), which is generally considerably greater in young children than in older children and adults (Table 2). Local anesthetics bind to plasma albumin and competition may occur with other drugs or biological products (especially bilirubin in neonates) bound to albumin. However, the principal binding protein of blood is an alpha1-glycoprotein (also termed orosomucoid), plasma concentration of which may be increased in disease states involving inflammatory disorders and malignancies (43). In infants under 9 months old, the plasma concentration of alpha1-glycoprotein is (as is that of albumin) low. This results in a relative increase of the unbound form of all amino-amide local anesthetics (43–46) and may lead to systemic toxicity for locals with high protein affinity (such as bupivacaine or etidocaine) (47–49).

Metabolism of local anesthetics. Aminoester local anesthetics are hydrolyzed mainly by plasma cholinesterase. Esterase activity is related to the developmental stage of the fetus and gradually increases throughout the first year of life (50); hydrolysis of procaine and chloroprocaine is thus reduced in infants (51). Most of the hepatic microsomal enzymatic systems necessary for the metabolism of aminoamide local anesthetics are present at birth but their activities are considerably lower than those in older patients (50,52–54). Hydroxylation rates of mepivacaine

Table 1. Peak Drug Concentrations (C_m) and the Time of Their Appearance (T_{peak}) of Some Frequently Used Local Anesthetics

Route and Agent	Age	Dose (mg/kg)	C_{max} ($\mu g/ml$)	T_{peak} (min)	$T_{\frac{1}{2}beta}$ (min)	Reference
Caudal:						
Lidocaine	7m–7yr	11	2.19 ± 0.25	45	NM	37
	3½yr–9yr	5	2.05 ± 0.08	28	155 ± 32	38
Mepivacaine	7m–7yr	11	2.53 ± 0.31	30	NM	37
Bupivacaine	7m–7yr	3.7	0.65 ± 0.08	30–45	NM	37
	5½yr–10yr	2.5	1.25 ± 0.09	29.1 ± 3.1	277 ± 34	39
Epidural:						
Bupivacaine	1yr–3yr	3	1.1	12–15	NM	40
	3yr–5yr	3	1.9	20	NM	40
	5yr–11yr	3	2.1	20	NM	40
Axillary:						
Bupivacaine	2yr–13yr	2	1.35 ± 0.37	22 ± 8	NM	41
	2yr–15yr	3	1.84 ± 0.45	22 ± 11	NM	41
Intercostal:						
Bupivacaine	3m–16yr	2	0.77 ± 0.25	5–10	160 ± 146*	42
	3m–16yr	3	1.27 ± 0.23	5–10	103 ± 75*	42
	3m–16yr	4	1.87 ± 0.5	5–10	123 ± 57*	42

m, months. yr, years. NM, not measured. *Calculated from reference 42.

Table 2. Pharmacokinetics of Amide-Linked Local Anesthetics: Comparison of Distribution Parameters in Adults and Neonates

Local Anesthetic	V_{DSS} (l/kg)	Plasma Protein Binding (%)	Free Fraction of Drug (%)	
			Whole blood	Plasma
Lidocaine:				
Neonate	1.4–4.9	25	—	—
Adult	0.2–1.0	55–65	36	30
Mepivacaine:				
Neonate	1.2–2.8	36	—	—
Adult	0.6–1.5	75–80	22	20
Bupivacaine:				
Neonate	—	50–70	—	—
Adult	0.8–1.6	85–95	0.07	0.05
Etidocaine:				
Neonate	—	—	—	—
Adult	1.5–1.8	90–95	0.09	0.05

and lidocaine are reduced in young patients (55,56), and they may be further lowered by pathological conditions such as respiratory disorders or cardiac failure (57). Prilocaine requires special consideration since its biotransformation yields 6-hydroxytoluidine which may lead to severe methemoglobinemia in neonates and infants even when relatively low doses are administered.

Epidural and intrathecal administration of narcotics for providing long-lasting pain relief is gaining general acceptance in adults (58). It is not surprising that this trend has also influenced the field of pedi-

atric anesthesia. The administration of morphine epidurally (0.05 mg/kg) or intrathecally (0.010 to 0.025 mg/kg) has proved suitable in children (59–63). However, as in adults, the administration of morphine along the neuraxis results in adverse effects in 50% of pediatric patients, including pruritus, nausea and vomiting, urinary retention and respiratory depression that may occur several hours after the administration of the narcotic. Respiratory depression can be prevented by continuous intravenous infusion of small amounts of naloxone, so small (5 $\mu g/kg/h$) they are not sufficient to reverse the analgesic effect of the narcotic (64–66). This continuous infusion is especially recommended when narcotics have been administered intraoperatively, and the patient's respiratory parameters should be monitored for the 24 hours postoperatively.

Although the pharmacology of local anesthetics is generally the same in children as it is in adults, there are differences related to enzyme immaturity, volumes of distribution and protein binding of the local anesthetics (47). In addition, the smaller fat content (15% of body weight) and skeletal mass (25% of body weight), the larger contribution of brain and liver to body weight, the higher cardiac output and regional blood flow result in pharmacokinetic differences between children and adults. However, clinically used local anesthetics can be metabolized even by neonates and dangers of systemic toxicity cannot be correlated to patient's age. Although the lower bind-

ing to plasma protein in young patients leads to a proportionately higher free drug in the blood, the distribution volume is significantly greater in children, with the result that the peak blood concentration is lower than in adults. Nevertheless, the risks of accumulation are generally increased in young patients, especially following repeated injections, since the mean elimination half life of local anesthetics is higher in infants.

Effects, Contraindications and Complications

Effects of regional blocks. Regional anesthesia, including epidural and spinal anesthesia, rarely results in hypotension in children less than 5 years old though slight but significant decreases in blood pressure (between 20 to 30% of control values) occur in older children (67–72). The negligible hemodynamic effects of major regional anesthesia has been ascribed to the immaturity of the sympathetic nervous system in infants and young children.

Epidural anesthesia is likely to suppress, in children as in adults, the markers of stress as represented by serum levels of ACTH, beta-endorphin, epinephrine and norepinephrine (73–75). In addition, regional anesthetic techniques may play a significant role in host defense mechanisms against various microorganisms (76–78), but this is controversial (79,80).

Complications. Some regional anesthetic techniques such as caudal blocks are easier to perform in children than in adults. Indeed, complications of caudal anesthesia are rare in children. Broadman et al. failed to detect any complication in 1154 consecutive caudal blocks in children (81).

Most local adverse effects result from incorrect needle placement rather than from the solution injected. Needle trauma and intraneural injection are normally accompanied by pain. Since most pediatric patients are lightly anesthetized with general anesthetics during the block procedure, this important sign is lost. However, deliberate transfixing of a nerve is, at least in animals, difficult, especially when the neurovascular bundles are mobile (82). The use of short beveled needles and techniques for precisely locating the tip of the needle would make direct injury to nerve bundles virtually impossible.

Regional adverse effects of injection of local anesthetics are a result of nerve conduction blockade. Mainly observed following epidural and spinal anesthesia, they include: 1) hypoventilation secondary to respiratory muscle paralysis (spread of the block to the cervical spinal segments); 2) urinary retention

following caudal epidurals; and 3) complications due to sympathetic blockade: hypotension (in patients more than 5 years old), Horner's syndrome and hypoglycemia.

Systemic toxicity is the most frequent complication of regional anesthetics (83,84). Local anesthetics entering the blood flow produce adverse effects primarily on the central nervous system: drowsiness, tinnitus, visual disturbances, dysarthria and muscular twitches, convulsion, coma, respiratory and circulatory depression. The danger of systemic toxicity can be reduced by observing basic safety rules, including aspiration to assure the tip of the needle is not in a blood vessel, injection of test doses and slow speed of injection.

Contraindications. The contraindications to regional anesthesia in children are much the same as in adults. They include: 1) infection at the site of puncture, septicemia, meningitis (central blocks); 2) bleeding disorders, including anticoagulant therapy (unusual in children); 3) allergy to local anesthetics (also unusual condition); 4) uncorrected hypovolemia (central blocks); and 5) degenerative axonal diseases (both central and peripheral).

Regional anesthesia should also be avoided when there is a danger of compressive disorders in closed fascial compartments, especially if a plaster cast does not allow accurate evaluation of the vascular status of an extremity. Parental refusal of regional blocks and psychoneurotic disorders must be considered absolute contraindications to both peripheral and central blocks.

Practice of Regional Anesthesia in Children

Selection of materials and techniques. The main factors to be taken into consideration are: 1) the site of the operation, including any areas involved in the surgical procedure (such as the site where a tourniquet is to be placed or where skin or bone grafts are to be taken); 2) the duration of pain relief sought; 3) the physical condition of the patient and the local conditions at the site of puncture; 4) the position of the patient required for performing the block; and 5) the experience of the anesthesiologist. It is wise to adjust the regional procedure to the demands of the surgical procedures; minor surgery should not be performed under spinal or epidural anesthesia [though spinal anesthesia has occasionally been recommended for minor procedure in healthy patients up to 13 years old (85)].

Difficulties may be encountered in attempting to locate nerve trunks or spinal spaces in children as in

Table 3. Recommended Agents And Doses for Block Procedures in Children

Local Anesthetic	Concentration (%)	Type of Block	Usual Doses (mg/kg)		Efficacy of E		Latency (min)	Duration (hours)	Motor Block
			With E	Without E	Latency	Duration			
Ester-linked:									
Chloroprocaine	2–3	Epi + Periph	10	7	±	+	7–15	0.5–1	±
Tetracaine	0.1–0.2	*Only spinal*	2	2	–	±	20–30	1.5–3	+
Amide-linked:									
Lidocaine	0.5–2	Epi + Periph	7.5	5	±	+ +	10–15	0.8–2	+
	5	*Only spinal*	1–2.5	1–2	–	±	7–10	1–1.5	+
Mepivacaine	1–2	Epi + Periph	6–8	5–7	±	+	10–15	1–1.25	+
Bupivacaine	0.25–0.5	Epi + Periph	2–3	2–3	–	(1)	20–30	2.5–6	±
Etidocaine	0.5–1	Epi + Periph	4–5	3–5	+	+	5–10	2–5	+ +

E, Epinephrine. Epi, Epidural blocks. Periph, Peripheral blocks. (1) Epinephrine improves the duration of peripheral blocks but not that of epidural blocks.

adults. This should be explained to the patient and his/her family at the preoperative visit, as should possible alternate procedures if such difficulties occur. If a first attempt at initiation of a regional anesthesia is unsuccessful, the position and the landmarks should be re-evaluated before another attempt is made. In any case, it is unreasonable to try to perform the same procedure more than three times.

Selection of anesthetic agents. A single local anesthetic cannot provide satisfactory blockade in every circumstance. While no local anesthetic is generally contraindicated in children, prilocaine and mepivacaine should not be used in small infants. Recommended dosages of some of the more suitable agents are shown in Table 3.

Addition of epinephrine to the local anesthetic decreases the rate of vascular uptake, i.e., decreases peak blood concentration and, therefore, the toxicity. Epinephrine may also increase the duration of action and intensity of blockade, especially with short-acting agents (lidocaine) and when low concentrations are used. However, epinephrine may result in ischemic disorders and gangrene if the local anesthetic is administered in areas supplied by terminal arteries (penile blocks, digital nerve blocks).

The use of combinations of local anesthetics, though gaining more acceptance in recent years, remains controversial. The main advantages expected from such mixtures are: 1) compensation of the limitations of each agent (e.g., mixing a local anesthetic with rapid onset but short duration of action with a local anesthetic with slow onset but long duration to achieve, one hopes, rapid onset of long-lasting regional anesthesia); and 2) reduction of the hazards of systemic toxicity by producing low and separated peak blood concentrations of each agent.

Selection of materials. While a variety of needles can be used in children for performing either peripheral or central blocks, only a small number of single-use needles should be used so that the anesthesiologist can gain experience in using them (especially the sensation felt during their insertion).

For proximal nerve blocks, 50 and 100 mm long insulated needles are suitable in over 95% of pediatric patients (only anterior and lateral sciatic nerve blocks in large patients may require needles longer than 100 mm). Local infiltration and field blocks may be performed with a 21 to 23 gauge 30 to 50 mm standard needle. Intradermal wheals are performed using a short (less than 30 mm) and fine (25 to 27 gauge) needle.

Caudal blocks may be performed with virtually any type of needle or plastic cannula. However, the use of a specific caudal needle with a short bevel and no longer than 30 mm, improves the conditions for approaching the epidural space and reduces the frequency of adverse effects. Spinal anesthesia may be performed using lumbar tap needles (22 gauge) or, preferably, either standard spinal needle (24 or 25 gauge) or Whitacre spinal needles (22 to 24 gauge).

Lumbar (and thoracic) epidural blocks may also be performed using several types of needles, but especially useful are Tuohy and Crawford needles. At least two sizes of epidural needle should be available: 20 gauge 40–50 mm needles for use in infants and young children; and 18 gauge 90–100 mm needles for use in patients over 7–8 years of age. Two types of epidural catheters should also be available for insertion in the two types of epidural needles.

Selection of an appropriate blocking procedure. In pediatrics, regional techniques are usually performed for improving the comfort of the patient, even though not absolutely necessary for the completion of the operation. Therefore, the techniques must not be potentially detrimental to the patients. To insure safety, it is important to use precise techniques for ascertaining the position of the tip of the needle as well as for injecting the anesthetic solution.

Eliciting paresthesias is widely used for locating nerve trunks in adults. The concept of paresthesias is

hard to explain to children. In addition, the safety of the procedure may be questionable as nerve lesions have been reported in adult patients who felt paresthesias during block procedures (86). Furthermore, since most pediatric patients are under light general anesthesia during induction of regional anesthesia, the nerves should be located using a technique that does not require the child's participation. This is best achieved by eliciting muscle twitches with a nerve stimulator adjusted to deliver 2 mA impulses every second.

A loss-of-resistance technique using a syringe filled with either air or normal saline solution is widely used for identifying the epidural space. The most dependable is the air-detection technique, especially in neonates and infants whose tissues are less densely packed and more hydrated than in older patients. However, the injection of air into the epidural space results in epidural bubbles which may occasionally prevent contact between local anesthetics and some root fibers, thus resulting in "gaps" in anesthesia in areas that would normally be anesthetized (87). Therefore, in patients over two years of age, fluid-filled syringes are preferred for use in the loss-of-resistance identification of the epidural space.

Technique of injection. The technique of injection is highly important and must include assurance that four basic safety rules are routinely followed whatever type of block or technique used:

1. aspiration must be performed prior to any injection,
2. the effects of a test dose (0.5 to 1 ml) on the vital functions (including tachycardia and arrhythmias when the anesthetic solution contains epinephrine) must be evaluated 30 to 60 seconds before injecting the total dose,
3. injection must be slow and performed at the same rate, between 90 and 120 seconds, whatever the volume;
4. aspiration tests must be repeated from time to time during injection to verify that the tip of needle has not moved and pierced a vessel.

Safety Conditions

Sedation of the patient. Emergency procedures in children with a full stomach may be performed under regional blocks as the sole anesthetic regimen. In most elective procedures, however, it is unusual that the patient requests a regional procedure as the sole anesthetic. The anesthesiologist may explain the advantages of regional anesthesia with regard to the

preservation of consciousness, ability to eat and drink in the immediate postoperative period, earlier ambulation and discharge, but most children usually prefer to be unconscious during both anesthetic and surgical procedures. The administration of sedatives or light general anesthesia are widely accepted techniques in pediatrics for performing block procedures (88). After completion of the block, general anesthesia may be discontinued or, more usually, maintained at very light levels (0.25 to 0.5% halothane in 65/35% N_2O/O_2). The same monitoring procedures as for general anesthesia are recommended.

Assessment of the block. Evaluating the efficacy of a regional block is not easy in children, even when conscious, if a motor block has not been produced. In alert patients, it is essential that 1) the anesthesiologist has gained the confidence of the child; 2) the patient cannot see what the anesthesiologist is doing; and 3) comparable tests for evaluation of anesthesia be performed in non-blocked areas. Skin pinching, usually considered most reliable, allows appropriate evaluations in most primary school patients, though the answers of adolescents may be far less reliable due to anxiety. The use of a nerve stimulator and the development of a motor block usually reassure most anxious patients that the block is effective. It is essential for the anesthesiologist to provide psychological support to the patient during the first 3 to 5 minutes following incision until he/she gains sufficient confidence in the efficacy of the block procedure.

Paradoxically, lightly anesthetized patients are more easily evaluated for distribution and depth of analgesia than alert patients. Consistent skin pinching is well tolerated in anesthetized areas while movement and other adverse effects occur when pain or discomfort occurs in unanesthetized areas. However, the assessment of the block often remains difficult and imprecise.

Technical Considerations

Upper Limb Blocks

Supraclavicular blocks. Supraclavicular blocks are suitable for emergency procedures of the upper extremities, especially when the lesions are located on the proximal part of the arm. In elective surgery, supraclavicular blocks are recommended 1) more often for postoperative than intraoperative pain relief; 2) when a tourniquet has to be placed on the proximal part of the arm; and 3) when the axillary route is not suitable. Contraindications (see following) are related to potential impairment of ventilation. Supraclavicular

blocks should be avoided in patients with respiratory insufficiency or in those requiring bilateral blocks.

The brachial plexus traverses the interscalene space in a perineurovascular compartment which ends at the level of the coracoid process of the scapula (there is no communication with the axilla) (17,18). Three basic techniques are suitable.

The interscalene approach according to Winnie (89) provides good sensory blockade of both cephalad nerves of the plexus and, in most patients, the lower branches of the cervical plexus; caudad branches of the brachial plexus may, however, be poorly anesthetized (90). This block may rarely result in severe adverse effects including vascular complications (especially vertebral artery injury), undesirable nerve blocks (phrenic nerve, recurrent laryngeal nerve, stellate ganglion block with Horner's syndrome) (91–94), and epidural or intrathecal penetration (particularly when the needle is advanced in a horizontal plane instead of slightly caudally) (95).

Several peri-subclavian artery approaches have been described (91,96–98). They consist of penetrating the lower part of the interscalene space, slightly above the first rib following various insertion routes and landmarks. These techniques provide good sensory blockade of virtually all branches of the brachial plexus (18,99). However, they require considerable experience for use in children and complications include pneumothorax, undesired block of other nerves, and subclavian vessel penetration (100–102). They should not be used routinely.

The parascalene approach (18) consists of penetrating the interscalene space away from the apical pleura and following an insertion route that would avoid encountering the great vessels, vagus and phrenic nerves, stellate ganglion, and epidural and subarachnoid spaces. The depth at which the plexus is located in children is shown in Fig. 4. Volumes of anesthetic solution that are usually injected are shown in Table 4. The anesthetized area is that supplied by both infra- and supraclavicular branches of the brachial plexus. The lower branches of the cervical plexus are blocked in more than 50% of procedures. Adverse effects are infrequent with this procedure, the most frequent being Horner's syndrome (in less than 5% of patients).

Axillary blocks. Axillary blocks are recommended for emergency procedures and elective surgery on the upper extremities, especially when surgery involves the forearm or the hand. This block procedure should be the first one thought of when regional anesthesia is being considered for an operation on the upper extremity. Contraindications include: 1) the presence of lymphadenopathies (infection, malignancies) in
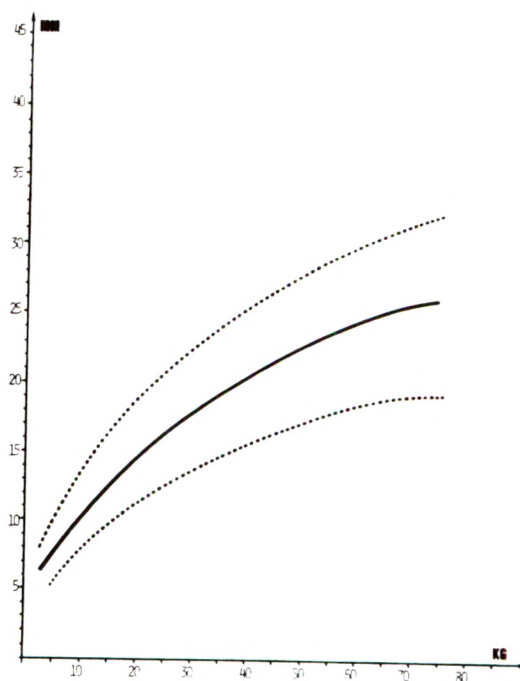
Figure 4. Depth (in mm) at which the brachial plexus can be found via the parascalene route according to patient's weight (in kg).

the axilla, 2) unstable fractures or lesions in which the shifting of the upper extremity is prohibited, and 3) proximal lesions (or placement of a tourniquet at the proximal part of the limb).

Axillary blocks are virtually free of complications. Accidental (or deliberate, in some techniques) arterial puncture is the most undesirable occurrence, which may occasionally result in transient vasculary insufficiency and/or compressive hematomata (103–106). Pneumothoraces have been observed following inappropriate insertion routes, but they are unusual.

Several methods have been recommended for axillary blocks (107–113). The use of a tourniquet aimed at favoring an upward flow of the local anesthetic (113) should be discouraged in children due to dangers of compression. Transaxillary artery approaches (111,112) should not be used in children since they may result in compressive hematomas. Some authors recommend a two-injection technique (109,111), one above, the other below the axillary artery. This procedure is not usual in children and may result in the injection of excessive amounts of local anesthetics.

Recommended volumes of anesthetic solution are shown in Table 4. The expected anesthetized area is the one that is supplied by the ulnar, median and radial nerves. However, in up to 40% of procedures, the spread of the local anesthetic to the radial nerve, and, at times, the ulnar nerve, is insufficient for complete surgical anesthesia (99).

Block Procedure	Recommended Volume of Anesthetic Solution According to the Weight of Children			
	below 20 kg	20–29 kg	30–45 kg	over 45 kg
Supraclavicular block	0.5–1 ml/kg	15–20 ml	20–22.5 ml	22.5–25 ml
Axillary block	0.3–0.6 ml/kg	10–15 ml	13–18 ml	18–20 ml
Femoral nerve block	0.5 ml/kg	10–12.5 ml	12.5–15 ml	15–17.5 ml
Sciatic nerve block	0.5 ml/kg	10–12.5 ml	12.5–15 ml	15–17.5 ml
"3-in-1" block	1 ml/kg	20–25 ml	25–30 ml	30–35 ml
Lumbar plexus block	0.7 ml/kg	10–12.5 ml	12.5–15 ml	15–17.5 ml

Other types of upper limb blocks. Intravenous regional anesthesias (Bier blocks) are suitable in children for operations on the upper extremities, distal to an inflated tourniquet (114–117). Contraindications include operations lasting more than about 90 minutes and lesions that do not permit: 1) the use of a tourniquet (such as extensive wounds or ischemic disorders); 2) the movement of the limb; and 3) the application of an Esmarch bandage (this is not an absolute contraindication). Also, patients with a history of convulsive disorders and/or various diseases including cardiac dysrhythmia, septicemia, hypovolemia, sickle cell disease and related disorders, and neurological or vascular disorders, should not have Bier blocks.

The safety and reliability of Bier blocks in children (114–117) include especially assurance that the tourniquet does not deflate. If this happens, the dangers of systemic toxicity are great, and several fatalities have been reported, including at least one reported case in children (118).

Distal conduction blocks at the shoulder, elbow or wrist are only complementary blocks in pediatrics and their indications are usually failure of proximal blocks (especially axillary blocks). These blocks are not usual in children and require fairly extensive experience. Their description can be found in reference 119.

Lower Limb Blocks

Femoral nerve block. Femoral nerve block is the lower limb block most often used in pediatrics. It is recommended for children with a fractured shaft of the femur and should be performed as early as possible after the accident for improving transport and physical and radiological examinations, wound dressings and orthopedic procedures (120,121). This block may also be used for intra- and postoperative pain relief in elective surgery of soft tissues of the thigh and operations on the femur especially, in the latter case,
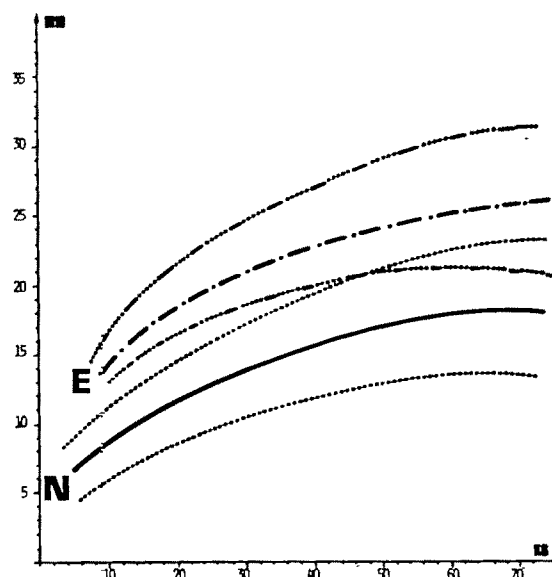
Figure 5. Depth (in mm) at which the femoral nerve can be found according to patient's weight (in kg). N = patients with a normal thigh. E = patients with enlarged thigh (hematoma due to fractured shaft of the femur).

when epidural blocks are not suitable. This block has no specific contraindications. Several techniques are suitable, as in adults (122–124) and the depth at which the nerve is located according to patient's weight is shown in Fig. 5.

Sciatic nerve blocks. Sciatic nerve blocks are recommended for operation on the foot and for extending the anesthetized area resulting from femoral blocks for procedures on the leg. There are no specific contraindications. Damage to the sciatic nerve has been reported following intramuscular injections in the dorsogluteal area (125–127), especially in infants, but both experimental data and clinical experience with the use of local anesthetics have confirmed the safety of the procedure (128,129).

The sciatic nerve is the largest nerve of the body. It may be blocked either proximally or immediately above its division (130,131) in the popliteal fossa (however, distal approaches are less usual in children

and should be considered complementary block procedures only). Basically, three proximal approaches are suitable. The most classical is the posterior approach, with the child lying on the contralateral side (122). An anterior approach has been described for use in patients placed in the dorsal recumbent position (132-135). This approach is more difficult and it is not free of complications (femoral vessels puncture). A lateral approach can also be used in patients lying supine (136,137) and it is safer and easier than the anterior approach. The depth at which the sciatic nerve is located depends on the insertion route (Figs. 6A-C). Recommended volumes of anesthetic solution are shown in Table 4.

Other peripheral nerve blocks of the lower extremities. The block of the lateral cutaneous nerve of the thigh (138,139) may be recommended for muscle biopsy (malignant hyperthermia) but it is usually performed for completing a femoral nerve block, especially for anesthetizing the incision site of operations on the femur.

The lumbar plexus can be blocked at the level of the psoas muscle where it lies in a fascial plane termed the "psoas compartment" (140). Two procedures have been reported (140-142) but the results are not the same: following Chayen's technique, the local anesthetic usually reaches the epidural space, thus providing anesthesia of both sides of the lower part of the body, whereas Winnie's technique results in unilateral sensory blockade of (ipsilateral) lumbar and sacral plexus nerves (141,142).

Other techniques. Obturator nerve and posterior femoral cutaneous nerve blocks have virtually no indications in pediatrics. The "3-in-1" block procedure may provide consistent blockade of the three main nerves of the lumbar plexus that supply the lower extremity (143). However, the procedure is not reliable and requires large amounts of local anesthetic. Peripheral nerve blocks at or below the knee have occasionally been used in children, but they, too, should be considered as unusual complementary blocks. A complete description of these block procedures can be found in reference 144. Intravenous regional anesthesia is not recommended for operations of the lower limbs in children.

Blocks Along the Neuraxis

Caudal blocks. Most surgical procedures of the lower part of the body (mainly below the umbilicus) can be performed under caudal anesthesia. The indications include especially herniorrhaphies, operations on the urinary tract, anus and rectum, and orthopedic procedures on the pelvic girdle and lower extremities (67,69,145-147). Specific contraindications include major malformations of the sacrum, myelomeningocele and meningitis.

Complications are unusual. They result from misplacement of the needle into superficial soft tissues (failure of the block), intravascular or intraosseous injections (systemic toxicity), subarachnoid injection (spinal anesthesia) or even penetration of pelvic viscera and vessels (148,149). These complications can be easily avoided by using a proper technique, including aspiration tests and evaluation of the effects of test doses. Hypotension may occur in patients more than 5 years old. A delay in voiding is frequently reported, but true urinary retention is rare. Vomiting has been reported in up to 30% of patients, but its occurrence is usually less [12% in our series (69), 5% in that of Busoni and Andreuccetti (150)]. Infection due to the proximity of the anus has almost never been reported unless an epidural catheter has been inserted via the caudal route. The most usual adverse effects are inappropriate extents of anesthesia (excessively low or high level of blockade, lateralization) and failures of the block, especially in children over 7 years of age. The latter complication occurs in 2.8% (67) to 23.2% (148) of attempted caudal blocks.

The epidural space can be entered less than 20 mm from the skin almost always (69). The optimal volume of local anesthetic to be administered is controversial, and several mathematical models and equations have been presented (21,148,150-158). From a practical point of view, the scheme recommended by Armitage is the most appropriate (159). The injection of 0.5, 1.0, and 1.25 ml/kg of local anesthetic provides an upper limit of analgesia lying at sacral-lumbar, lumbar-thoracic, and mid-thoracic levels, respectively.

Intervertebral epidural blocks. Epidural anesthesia may be used as the sole anesthetic (emergency procedures) or in combination with general anesthesia for operations of the lower extremities and almost any part of the trunk, including the chest, abdominal cavity, pelvis and retroperitoneal areas (68,159-165). Deciding whether the caudal or either the lumbar or sacral intervertebral approaches should be used may be difficult. Most operations on the pelvis and lower limbs in young children (less than 7 years old) are preferably performed under caudal anesthesia, provided that a single injection technique is adequate. Conversely, procedures in older patients or those of long-duration (especially orthopedic procedures) benefit greatly from the placement of an epidural catheter which can only be safely inserted in the lumbar (or, to a lesser extent, thoracic) areas.
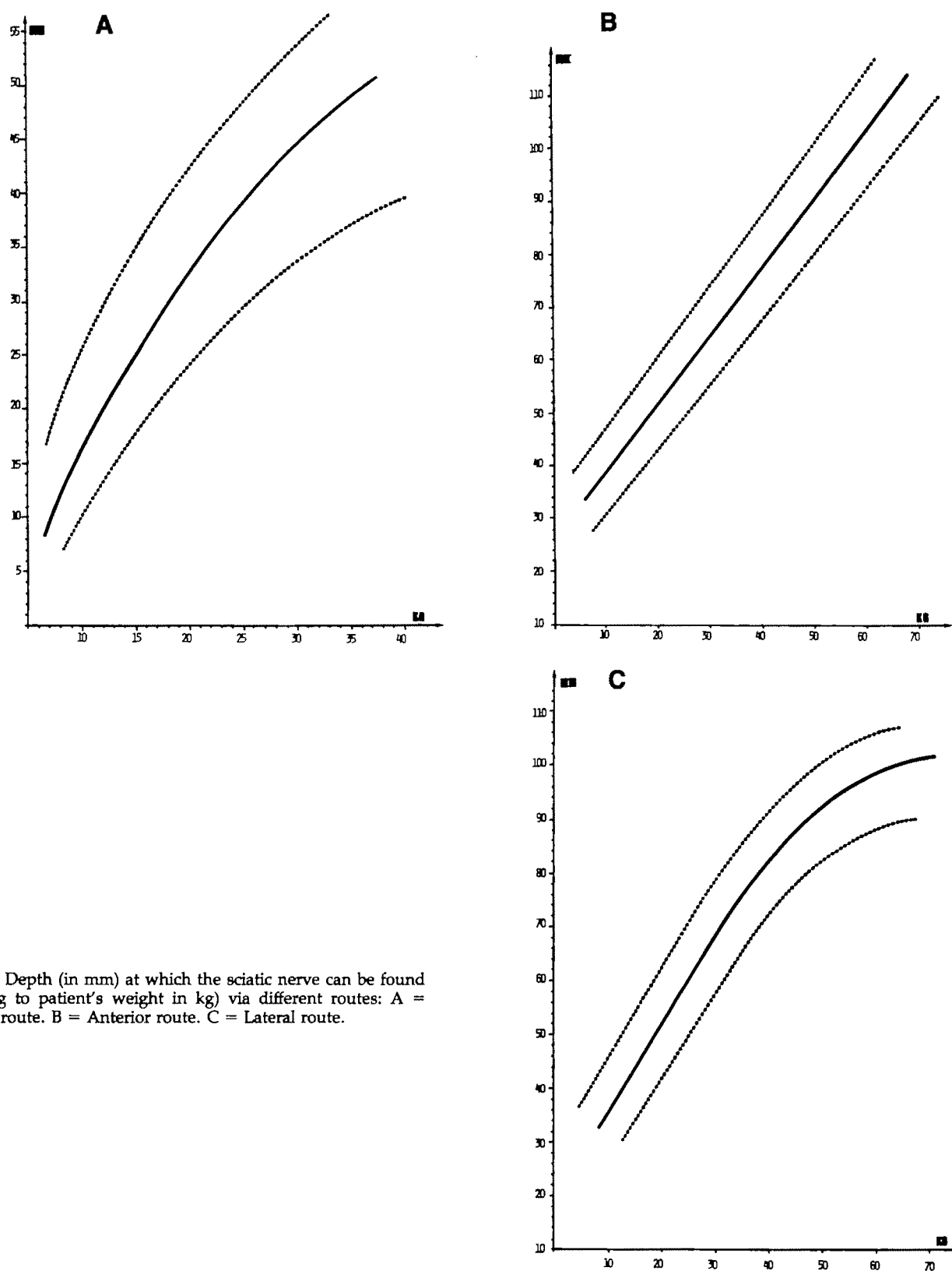
Figure 6. Depth (in mm) at which the sciatic nerve can be found (according to patient's weight in kg) via different routes: A = Posterior route. B = Anterior route. C = Lateral route.

Specific contraindications include severe malformations of the vertebral column and the spinal cord (complete spina bifida, meningocele). Also, patients with a history of hydrocephalus or severe convulsive disorders, and those with vertebral implants (Harrington rods), reduced intracranial compliance orele

vated intracranial pressure should preferably not be given epidural anesthesia.

Several complications may occur following epidural blocks in children. They are basically the same as in adult patients. Accidental puncture of epidural vessels may lead to ischemic disorders and/or systemic toxicity. Direct trauma of the spinal cord may occur following thoracic and upper lumbar approaches. Neurological disorders and sequelae have been reported in adult patients (166–168): fortunately, they are extremely unusual in children. Also, epidural catheters may be inappropriately placed or ruptured (169–171). Complete failure of the block is usually the result of the misplacement of the needle (or catheter). Inadequate sensory blockade is not unusual and may consist of low or excessive spread of analgesia, lateralization of the block or persistence of unblocked segments. The use of epidural narcotics may be associated with several complications, especially delayed respiratory depression (172–174), thus requiring postoperative monitoring of respiratory parameters.

Epidural techniques are basically the same in children as in adults. Difficulties may be encountered during the procedure due to inappropriate place or route of insertion of the needle and insufficient flexion or deformities of the vertebral column. If the anesthesiologist has had experience with this technique, the oblique paramedian approach may be attempted. In some patients, epidural blocks may be performed at thoracic levels for operations on the chest and/or the upper part of the abdomen (162,164). Midline insertion routes are suitable in most pediatric patients. When difficulties are encountered, it may become necessary to use the oblique paramedian route. Whatever the route used, thoracic approaches are more hazardous than lumbar epidural blocks: they should be attempted only by experienced anesthesiologists. Cervical epidural blocks have not been reported in children. Recently, Busoni and Sarti (165) reported a new technique for approaching the epidural space via S1–S2 or S2–S3 interspaces. This procedure is a suitable alternative to caudal blocks, especially when the sacral hiatus is difficult to locate by palpation.

The distance between the skin and the epidural space depends on the angle of insertion of the needle and patient's weight (Figs. 7A–C). As with caudal anesthesia, several formulas have been reported for the volume of anesthetic solutions to be injected epidurally. From a practical point of view, the most dependable scheme of administration is that recommended by Schulte-Steinberg (21):

$$V = 1/10 \times \text{(age in years)}$$

where V is the volume (in ml) necessary to block one spinal segment.

Spinal anesthesia. Present indications for spinal anesthesia in pediatric patients include surgery of the lower part of the body in high-risk infants, especially premature infants who experienced respiratory distress syndromes in the neonatal period and patients with potentially life-threatening anomalies (tracheomalacia, Pierre Robin syndrome, arthrogryposis multiplex congenita, severe hypotrophy, macroglossia) (71,72,85,160). The aim of spinal anesthesia is to provide adequate distribution of anesthesia with very small amounts of local anesthetic while avoiding intubation and respiratory assistance.

Larger children undergoing major operations (open heart surgery, spinal fusions) may benefit from the administration of intrathecal narcotics (59,63). However, careful postoperative monitoring is necessary due to risks of delayed respiratory depression.

Spinal anesthetics have the same contraindications as epidural blocks. The duration of sensory blockade does not allow performance of operations lasting over about 90 minutes. In addition, spinal anesthesia in children should not be considered a routine procedure and must not be performed by novices.

The technique consists of performing a lumbar puncture. The same positions as for lumbar epidural blocks are suitable. However, the recommended position in high-risk infants is the lateral decubitus with the chin extended (175,176). Local anesthetics, usually in hyperbaric solutions, such as 0.5% dibucaine, 5% lidocaine, 1% tetracaine, 0.75% and 0.5% bupivacaine have been used with success in children. Tetracaine may be the best choice at present (177–178) though 0.5% bupivacaine in isobaric solution has also proven suitable (179).

Other Regional Procedures

Intercostal nerve blocks. Intercostal nerve blocks may be used for relieving pain during and after thoracotomy, liver transplantation, pleural drainage and in patients with rib fractures. They are not recommended for patients with a pulmonary disease impairing blood-gas exchanges, and for patients who cannot be kept under intensive medical observation for several hours (due to danger of clinically delayed pneumothoraces). While the intercostal space can be approached from virtually any point along the lower border of the ribs, the most usual sites of puncture are on the midaxillary line with the child lying semi-prone (180).
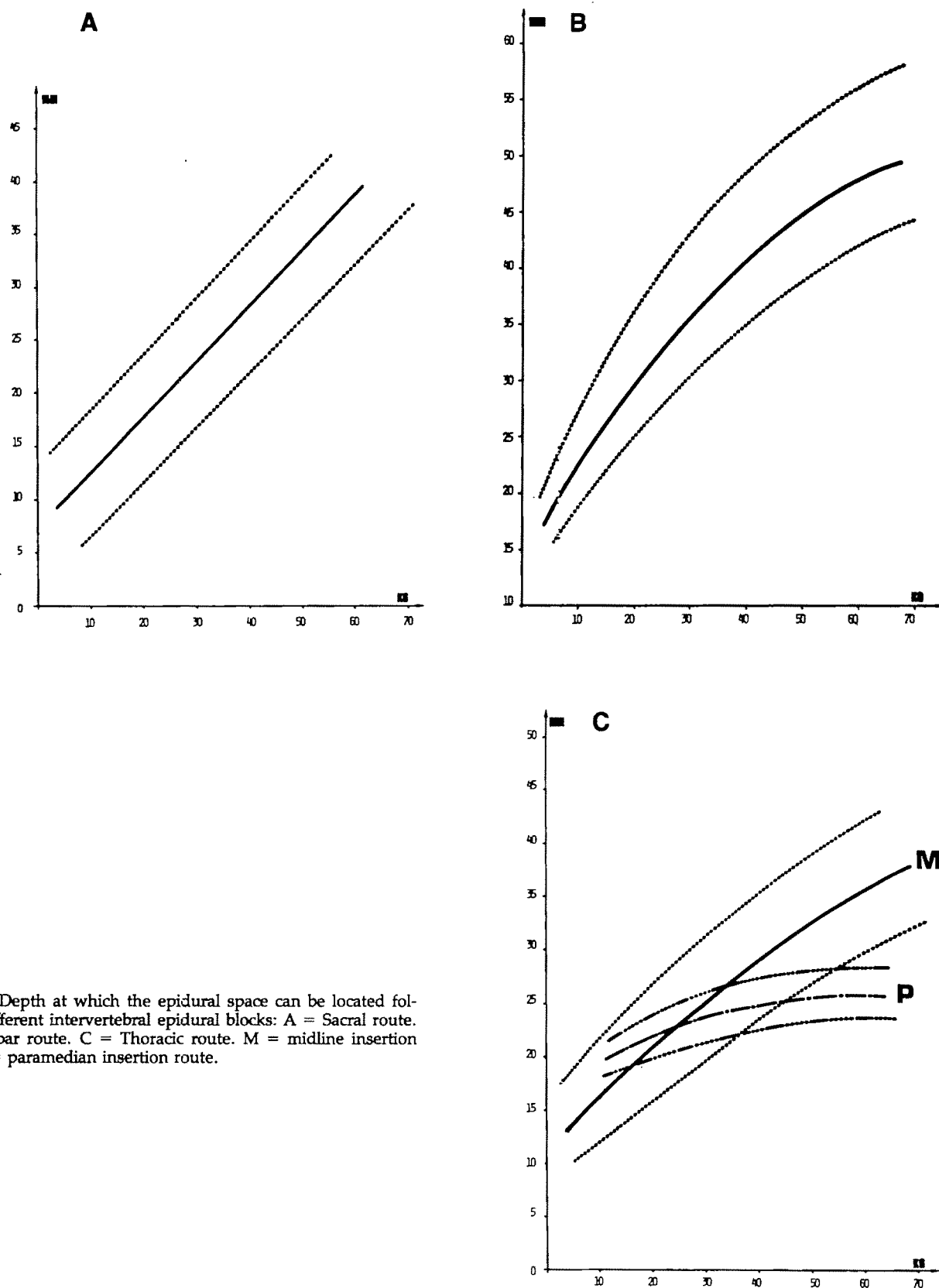
Figure 7. Depth at which the epidural space can be located following different intervertebral epidural blocks: A = Sacral route. B = Lumbar route. C = Thoracic route. M = midline insertion route. P = paramedian insertion route.

Usually, several adjacent intercostal nerves have to be blocked so that an appropriate sensory blockade can develop. Intercostal block is the block technique which leads to the highest blood concentrations of local anesthetics for a given dose (42,181); therefore only diluted solutions should be injected (1 ml per intercostal space of bupivacaine diluted so that the total dose does not exceed 2 mg/kg).

Ilioinguinal and iliohypogastric nerve blocks. These nerve blocks may provide adequate pain relief for operations on the inguinal region (182–184) but the technique is less reliable than caudal anesthesia.

Penile blocks. Several procedures have been recommended for providing postoperative pain relief after operation of the penis. Administration of parenteral narcotics does not always guarantee appropriate pain relief (185,186). Caudal blocks are effective but may result in adverse effects such as vomiting and delayed micturition (187); furthermore, performing a central block for minor surgery seems to many to be unnecessary. Topical anesthesia (188,189) is very simple, can be repeated and is said to be safe (but data on vascular uptake and peak blood concentration are not available); however, it is not very reliable and potential bacterial contamination is not unlikely.

Since all the structures of the penis (except its base) are supplied by the two dorsal nerves of the penis, penile blocks may be the most dependable technique for providing postoperative pain relief following surgery of the penis. This can be achieved either at random, by a "subcutaneous" ring of local anesthetic (190) or more accurately by a specific block of the dorsal nerves of the penis (191–193). Blind injections, especially dorsally in the midline, may damage the dorsal vessels of the penis, with potential risks of systemic toxicity and compressive hematomas. On the other hand, dorsal nerve blocks using the technique of Soliman and Tremblay (191) are technically difficult: a surgical level of anesthesia is not obtained in a number of procedures and complications as severe as gangrene of the glans penis have been reported (194). Therefore, none of the techniques mentioned above can be recommended without some reservations and this author believes that the dorsal nerves of the penis should be approached via the subpubic space since this technique requires little amounts of local anesthetic and appears easy, safe and reliable (195).

Conclusion

The use of regional anesthetic techniques in children is gaining more general acceptance in recent years.

This increasing interest results from the considerable technical improvements which have been made, including the use of nerve stimulators for precise location of nerve trunks and the availability of equipments designed specifically for children. In addition, greater acceptance and use of regional procedures in pediatrics are a consequence of 1) a better understanding of the basic anatomical, physiological and pharmacologically relevant differences between children and adults, and 2) a broader definition of anesthesia in which general and regional procedures are considered complementary rather than opposite. The selection of an anesthetic procedure, either general, regional or a combination of both, is made on a case-by-case evaluation of what is best for a given patient.

References

1. Bier A. Versuche über Cocainiserung des Ruckenmarks. Deutsch Zeit Chir 1899;51:361–9.

2. Bainbridge WS. A report of twelve operations on infants and young children during spinal anesthesia. Arch Pediatr 1901; 18:510–20.

3. Gray HT. A study of spinal anaesthesia in children and infants from a series of 200 cases—I. Lancet 1909;II:913–7.

4. Gray HT. A study of spinal anaesthesia in children and infants from a series of 200 cases—II. Lancet 1909;II:991–5.

5. Farr RE. Local anesthesia in infancy and childhood. Arch Pediatr 1920;37:381–3.

6. Campbell MF. Caudal anesthesia in children. Am J Urol 1933; 30:245–9.

7. Lourey CJ, McDonald IM. Caudal anaesthesia in infants and children. Anaesth Intensive Care 1973;1:547–8.

8. Kay B. Caudal blocks for postoperative pain relief in children. Anaesthesia 1974;29:610–1.

9. Melman E, Penuelas J, Marrufo J. Regional anesthesia in children. Anesth Analg 1975;54:387–90.

10. Carpenter MB. Development and histogenesis of the nervous system. In: Carpenter MB, ed. Human Neuroanatomy, 7th ed, Chapter 3. Baltimore: Williams & Wilkins, 1976:49–70.

11. Larroche JC. Développement du système nerveux. Aspects morphologiques. In: Boué A, Henrion R, David G, eds. Développement prénatal normal et pathologique. Paris: Flammarion, 1980:275–85.

12. Williams PL, Warwick R. Embryology: Nervous system and special sense organs. In: Williams PL, Warwick R, eds. Gray's Anatomy, 36th ed. Philadelphia: WB Saunders, 1980:156–80.

13. Kandt RS, Johnston MV, Goldstein GW. The central nervous system: basic concepts. In: Gregory GA, ed. Pediatric Anesthesia, vol 1. New York: Churchill Livingstone, 1983:129–67.

14. Wildsmith JAW. Peripheral nerve and local anaesthetic drugs. Br J Anaesth 1986;58:692–700.

15. O'Rahilly R, Meyer DB. The timing and sequence of events in the development of the human vertebral column during the embryonic period proper. Anat Embryol 1979;157:167–76.

16. O'Rahilly R, Benson DR. The development of the vertebral column. In: Bradford DS, Hensinger RN, eds. The Pediatric Spine. New York: Thieme Inc, 1985:3–17.

17. Vester-Andersen T, Broby-Johansen U, Bro-Rasmussen F. Perivascular axillary block VI: the distribution of gelatine solution injected into the axillary neurovascular sheath of cadavers. Acta Anaesthesiol Scand 1986;30:18–22.

18. Dalens B, Vanneuville G, Tanguy A. A new parascalene approach to the brachial plexus in children: comparison with the supraclavicular approach. Anesth Analg 1987;66:1264–71.

19. Savolaine ER, Pandya JB, Greenblatt SH, Conover SR. Anatomy of the human lumbar epidural space: new insights using CT-epidurography. Anesthesiology 1988;68:217–20.

20. Schulte-Steinberg O, Rahlfs VW. Spread of extradural analgesia following caudal injection in children—a statistical study. Br J Anaesth 1977;49:1027–34.

21. Schulte-Steinberg O. Regional anaesthesia for children. Ann Chir Gynaecol 1984;73:158–65.

22. Gouveia MA. Raquianestesia para pacientes pediatricos—experiencia pessoal em 50 casos. Rev Bras Anest 1970;20:501–4.

23. Dodson ME. Postoperative pain—physiology, natural history and psychology. In: Dodson ME, ed. The Management of Postoperative Pain (Current Topics in Anaesthesia n°8). London: Edward Arnold, 1985:1–30.

24. Owens ME, Todt EH. Pain in infancy: neonatal reaction to a heel lance. Pain 1984;20:77–86.

25. Owens ME. Pain in infancy: conceptual and methodological issues. Pain 1984;20:213–30.

26. Johnston CC, Strada ME. Acute response in infants: a multidimensional description. Pain 1986;24:373–82.

27. Thompson KL, Varni JW. A developmental cognitive-biobehavioral approach to pediatric pain assessment. Pain 1986;25:283–96.

28. Gaffney A, Dunne EA. Developmental aspects of children's definitions of pain. Pain 1986;26:105–17.

29. Lavigne JV, Schulein MJ, Hahn YS. Psychological aspects of painful medical conditions in children. I. Developmental aspects and assessment. Pain 1986;27:133–46.

30. Lavigne JV, Schulein MJ, Hahn YS. Psychological aspects of painful medical conditions in children. II. Personality factors, family characteristics and treatment. Pain 1986;27:147–69.

31. McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J, Chapman J. CHEOPS: a behavioral scale for rating postoperative pain in children. Advances in Pain Research and Therapy 1985;9:395–402.

32. Ross DM, Ross SA. Childhood pain: the school-aged child's viewpoint. Pain 1984;20:179–91.

33. Maunuksela EL, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. Clin Pharmacol Ther 1987;42:137–41.

34. Runciman WB, Mather LE, Ilsley AH, Carapetis RJ, McLean CF. A sheep preparation for studying interactions between blood flow and drug disposition. II: Experimental applications. Br J Anaesth 1984;56:1117–29.

35. Covino BG. Pharmacology of local anaesthetic agents. Br J Anaesth 1986;58:701–16.

36. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986;58:717–31.

37. Takasaki M. Blood concentrations of lidocaine, mepivacaine and bupivacaine during caudal analgesia in children. Acta Anaesthesiol Scand 1984;28:211–4.

38. Ecoffey C, Desparmets J, Berdeaux A, Maury M, Giudicelli JF, Saint-Maurice C. Pharmacokinetics of lignocaine in children following caudal anaesthesia. Br J Anaesth 1984;56:1399–402.

39. Ecoffey C, Desparmets J, Maury M, Berdeaux A, Giudicelli JF, Saint-Maurice C. Bupivacaine in children: pharmacokinetics following caudal anesthesia. Anesthesiology 1985;63:447–8.

40. Eyres RL, Hastings CL, Brown TCK, Oppenheim RC. Plasma bupivacaine concentrations following lumbar epidural anaesthesia in children. Anaesth Intensive Care 1986;14:131–4.

41. Campbell RJ, Ilett KF, Dusci L. Plasma bupivacaine concentrations after axillary block in children. Anaesth Intensive Care 1986;14:343–6.

42. Rothstein P, Arthur GR, Feldman HS, Kopf GS, Covino BG. Bupivacaine for intercostal nerve blocks in children: blood concentrations and pharmacokinetics. Anesth Analg 1986;65:625–32.

43. Wood M. Plasma drug binding: implications for anesthesiologists. Anesth Analg 1986;65:786–804.

44. Tucker GT, Boyes RN, Bridenbaugh PO, Moore DC. Binding of anilide-type local anesthetics in human plasma. Anesthesiology 1970;33:304–14.

45. Thomas J, Long G, Moore G, Morgan D. Plasma protein binding and placental transfer of bupivacaine. Clin Pharmacol Ther 1975;19:426–34.

46. Wood M, Wood AJJ. Changes in plasma drug binding and alpha1-acid glycoprotein in mother and newborn infant. Clin Pharmacol Ther 1981;29:522–6.

47. Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants—age-related differences and therapeutic implications. Clin Pharmacokinet 1980;5:485–527.

48. Nau H. Clinical pharmacokinetics in pregnancy and perinatology—L. Placental transfer and fetal side effects of local anaesthetic agents. Dev Pharmacol Ther 1985;8:149–81.

49. Kanto J. Obstetric analgesia—clinical pharmacokinetic considerations. Clin Pharmacokinet 1986;11:283–98.

50. Zsigmond EK, Downs JR. Plasma cholinesterase activity in newborns and infants. Can Anaesth Soc J 1971;18:278–85.

51. Finster M. Toxicity of local anesthetics in the fetus and newborn. Bull N Y Acad Med 1976;52:222–5.

52. DiFazio CA. Metabolism of local anaesthetics in the fetus, newborn and adult. Br J Anaesth 1979;51:29S–34S.

53. Eather KF. Regional anesthesia for infants and children. Int Anesthesiol Clin 1975;13:19–48.

54. Singler RC. Local and regional anesthesia. In: Gregory GA, ed. Pediatric Anesthesia (Vol 1). New York: Churchill-Livingstone, 1983:481–518.

55. Brown WU Jr, Belle GC, Lurie AO, Weiss JB, Scanlon JW, Alper MH. Newborn blood levels of lidocaine and mepivacaine in the first postnatal day following maternal epidural anesthesia. Anesthesiology 1975;42:698–707.

56. Mihaly GW, Moore RG, Thomas J, Triggs EJ, Thomas D, Shanks CA. The pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. I. Lignocaine. Eur J Clin Pharmacol 1978;13:143–52.

57. Haberer JP, Monteillard C. Effets de l'anesthésie péridurale obstétricale sur le foetus et le nouveau-né. Ann Fr Anesth Réanim 1986;5:381–414.

58. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.

59. Jones SEF, Beasley JM, McFarlane DWR, Davis JM, Hall-Davies G. Intrathecal morphine for postoperative pain relief in children. Br J Anaesth 1984;56:137–41.

60. Shapiro LA, Jedeikin RJ, Shavlev D, Hoffman S. Epidural morphine analgesia in children. Anesthesiology 1984;61:210–2.

61. Attia J, Ecoffey C, Sandouk P, Gross JB, Samii K. Epidural morphine in children: pharmacokinetics and CO_2 sensitivity. Anesthesiology 1986;65:590-4.

62. Dalens B, Tanguy A, Haberer JP. Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children. Anesth Analg 1986;65:1069-73.

63. Dalens B, Tanguy A. Intrathecal morphine for spinal fusion in children. Spine 1988;13:494-8.

64. Jones RDM, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. Br Med J 1980;281:645-6.

65. Thind GS, Wells JCD, Wilkes RG. The effects of continuous intravenous naloxone on epidural morphine analgesia. Anaesthesia 1986;41:582-5.

66. Rawal N, Schott U, Dahlstrom B, Inturrisi CE, Tandon B, Sjostrand U, Wennhager M. Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. Anesthesiology 1986;64:194-201.

67. McGown RG. Caudal analgesia in children—five hundred cases for procedures below the diaphragm. Anaesthesia 1982; 37:806-18.

68. Arthur DS, McNicol LR. Local anaesthetic techniques in paediatric surgery. Br J Anaesth 1986;58:760-78.

69. Dalens B, Hasnaoui A. Caudal anesthesia in pediatric surgery—success rate and adverse effects in 750 consecutive patients. Anesth Analg, in press.

70. Dohi S, Naito H, Takahashi T. Age related changes in blood pressure and duration of motor block in spinal anesthesia. Anesthesiology 1979;50:319-23.

71. Abajian JC, Mellish RWP, Browne AF, Perkins FM, Lambert DH, Mazuzan JE. Spinal anesthesia for surgery in the high-risk infant. Anesth Analg 1984;63:359-62.

72. Harnik EV, Hoy GR, Potolicchio S, Stewart DR, Siegelman RE. Spinal anesthesia in premature infants recovering from respiratory distress syndrome. Anesthesiology 1986;64:95-9.

73. Kehlet H. Epidural analgesia and the endocrine-metabolic response to surgery—updates and perspectives. Acta Anaesthesiol Scand 1984;28:125-7.

74. Giaufré E, Conte-Devolx B, Morrisson-Lacombe G, et al. Anesthésie péridurale par voie caudale chez l'enfant—etude des variations endocriniennes. Presse Méd 1985;14:201-3.

75. Dupont D, Velin P, Cabour F, Candito M, Rives E. Influence de l'anesthésie caudale sur la sécrétion des catécholamines chez l'enfant. Ann Fr Anesth Réanim 1987;6:156-8.

76. Schmidt RM, Rosenkrans HS. Antimicrobiological activity of local anaesthetics: lignocaine and procaine. J Infect Dis 1970; 121:597-607.

77. Hole A, Unsgaard G, Breivik H. Monocyte functions are depressed during and after surgery under general anaesthesia but not under epidural anaesthesia. Acta Anaesthesiol Scand 1982;26:301-7.

78. Rosenberg PH, Renkonen OV. Antimicrobial activity of bupivacaine and morphine. Anesthesiology 1985;62:178-9.

79. Cullen BF, Haschke RH. Local anesthetic inhibition of phagocytosis and metabolism of human leukocytes. Anesthesiology 1974;40:141-6.

80. Hammer R, Dahlgren C, Stendhal O. Inhibition of human leukocyte metabolism and random mobility by local anaesthesia. Acta Anaesthesiol Scand 1985;29:520-3.

81. Broadman LM, Hannallah RS, Norden RS, McGill WA. "Kiddie caudals": experience with 1154 consecutive cases without complications. Anesth Analg 1987;66:S18.

82. Selander D, Duhner KG, Lundborg G. Peripheral nerve injury due to injection needles used for regional anaesthesia—an experimental study of the acute effects of needle point trauma. Acta Anaesthesiol Scand 1977;21:182-8.

83. Scott DB. Toxic effects of local anaesthetic agents on the central nervous system. Br J Anaesth 1986;58:732-5.

84. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58:736-46.

85. Blaise GA, Roy WL. Spinal anaesthesia for minor paediatric surgery. Can Anaesth Soc J 1986;33:227-30.

86. Selander D, Edshage S, Wolff T. Paresthesiae or no paresthesiae? Nerve lesions after axillary blocks. Acta Anaesthesiol Scand 1979;23:27-33.

87. Dalens B, Bazin JE, Haberer JP. Epidural bubbles as a cause of incomplete analgesia during epidural anesthesia. Anesth Analg 1987;66:679-83.

88. Armitage EN. Regional anaesthesia in paediatrics. Clin Anaesthesiol 1985;3:553-68.

89. Winnie AP. Interscalene brachial plexus block. Anesth Analg 1970;49:455-66.

90. Vester-Andersen T, Christiansen C, Hansen A, Sorensen M, Meisler C. Interscalene brachial plexus block: area of analgesia, complications and blood concentrations of local anaesthetics. Acta Anaesthesiol Scand 1981;25:81-4.

91. Moore DC. Supraclavicular approach for block of the brachial plexus. In: Moore DC, ed. Regional block—A Handbook for Use in the Clinical Practice of Medicine and Surgery (4th ed.). Springfield: CC Thomas, 1981:221-42.

92. Kayerker UM, Dick MM. Phrenic nerve paralysis following interscalene brachial plexus block. Anesth Analg 1983;62:536-7.

93. Bashein G, Robertson HT, Kennedy WF jr. Persistent phrenic nerve paresis following interscalene brachial plexus block. Anesthesiology 1985;63:102-4.

94. Seltzer JL. Hoarseness and Horner's syndrome after interscalene brachial plexus block. Anesth Analg 1977;56:585-6.

95. Kumar A, Battit GE, Froese AB, Long MC. Bilateral cervical and thoracic epidural blockade complicating interscalene brachial plexus block: report of two cases. Anesthesiology 1971; 35:650-8.

96. Eriksson E. Brachial plexus block—supraclavicular approach. In: Eriksson E, ed. Illustrated Handbook in Local Anaesthesia. Copenhagen: Munksgaard, 1969:75-7.

97. Vongvises P, Panijayanond T. A parascalene technique of brachial plexus anesthesia. Anesth Analg 1979;58:267-73.

98. Dupré LJ, Danel V, Legrand JJ, Stieglitz P. Surface landmarks for supraclavicular block of the brachial plexus. Anesth Analg 1982;61:28-31.

99. Lanz E, Theiss D, Jankovic D. The extent of blockade following various techniques of brachial plexus block. Anesth Analg 1983;62:55-8.

100. Gordh T. Complications and their treatment. In Ref 96, 14-7.

101. Knoblanche GE. The incidence and aetiology of phrenic nerve blockade associated with supraclavicular brachial plexus block. Anaesth Intensive Care 1979;7:346-9.

102. Farrar MD, Scheybani M, Nolte H. Upper extremity block effectiveness and complications. Regional Anesth 1981;6:133-4.

103. Lennon RL, Linstromberg JW. Brachial plexus anesthesia and axillary sheath elastance. Anesth Analg 1983;62:215-7.

104. Merril DG, Brodsky JB, Hentz RV. Vascular insufficiency following axillary block of the brachial plexus. Anesth Analg 1981;60:162-4.

105. Sada T, Kobayashi T, Murakami S. Continuous axillary brachial plexus block. Can Anaesth Soc J 1983;30:201-5.

106. Ang ET, Lassale B, Goldfarb G. Continuous axillary brachial plexus block—a clinical and anatomical study. Anesth Analg 1984;63:680-4.

107. Accardo NJ, Adriani J. Brachial plexus block: a simplified technic using the axillary route. Southern Medical Journal 1949;42:920-3.

108. Eather KF. Axillary brachial plexus block. Anesthesiology 1958;19:683–5.

109. Burnham PJ. Simple regional nerve block for surgery of the hand and forearm. J Am Med Assoc 1959;169:941–3.

110. Winnie AP, Collins VJ. The subclavian perivascular technique of brachial plexus anesthesia. Anesthesiology 1964;25:353–63.

111. De Jonc RH. Axillary block of the brachial plexus. Anesthesiology 1961;22:215–25.

112. Moore DC. Axillary approach for block of the brachial plexus. In Ref 91, 243–56.

113. Eriksson E. Brachial plexus block—axillary approach. In Ref 96, 78–80.

114. Gingrich TF. Intravenous regional anesthesia of the upper extremity in children. J Am Med Assoc 1967;200:135–7.

115. Carrel ED, Eyring EJ. Intravenous regional anesthesia for childhood fractures. J Trauma 1971;11:301–5.

116. Fitzgerald B. Intravenous regional anaesthesia in children. Br J Anaesth 1976;48:485–6.

117. Rudzinski JP. Pediatric application of intravenous regional anesthesia. Regional Anesth 1983;8:69–72.

118. Heath M. Deaths after intravenous regional anaesthesias. Br J Anaesth 1982;285:913–4.

119. Dalens B. Distal conduction blocks. In: Dalens B, ed. Pediatric Regional Anesthesia. Boca Raton: CRC Press. In press.

120. Grossbard GD, Love BRT. Femoral nerve block: a simple and safe method of instant analgesia for femoral shaft fractures in children. Aust NZ J Surg 1979;49:592–4.

121. Berry FR. Analgesia in patients with fractured shaft of the femur. Anaesthesia 1977;32:576–7.

122. Moore DC. Block of the sciatic and femoral nerves. In Ref 91, 275–88.

123. Tondare AS, Nadkarni AV. Femoral nerve block for fractured shaft of femur. Can Anaesth Soc J 1982;29:270–1.

124. Khoo ST, Brown TCK. Femoral nerve block—the anatomical basis for a single injection technique. Anaesth Intensive Care 1983;11:40–2.

125. Combes MA, Clark WK, Gregory CF, James JA. Sciatic nerve injury in infants—recognition and prevention of impairment resulting from intragluteal injections. J Am Med Assoc 1960;173:1336–8.

126. Gilles FH, French JH. Postinjection sciatic nerve palsies in infants and children. J Pediatr 1961;58:195–7.

127. Johnson EW, Raptou AD. A study of intragluteal injection. Arch Phys Med 1965;46:167–70.

128. Kytta J, Heinonen E, Rosenberg PH, Wahlstrom T, Gripenberg J, Huopaniemi T. Effects of repeated bupivacaine administration on sciatic nerve and surrounding muscle tissue in rats. Acta Anaesthesiol Scand 1986;30:625–9.

129. Myers RR, Kalichman MW, Reisner LS, Powell HC. Neurotoxicity of local anesthetics: altered perineural permeability, edema, and nerve fiber injury. Anesthesiology 1986;64:29–35.

130. Rorie DK, Byer DE, Nelson DO, Sittipong R, Johnson KA. Assessment of block of the sciatic nerve in the popliteal fossa. Anesth Analg 1980;59:371–6.

131. Kempthorne PM, Brown TCK. Nerve blocks around the knee in children. Anaesth Intensive Care 1984;12:14–7.

132. Beck GP. Anterior approach to sciatic nerve block. Anesthesiology 1963;24:222–4.

133. Magora F, Pessachovitch B, Shoham I. Sciatic nerve block by the anterior approach for operations on the lower extremity. Br J Anaesth 1974;46:121–3.

134. Raj PP, Parks RI, Watson TD, Jenkins MT. A new single-position supine approach to sciatic-femoral nerve block. Anesth Analg 1975;54:489–93.

135. McNicol LR. Sciatic nerve block for children—sciatic nerve block by the anterior approach for postoperative pain relief. Anaesthesia 1985;40:410–4.

136. Ichiyanagi K. Sciatic nerve block: lateral approach with the patient supine. Anesthesiology 1959;20:601–4.

137. Guardini R, Waldron BA, Wallace WA. Sciatic nerve block: a new lateral approach. Acta Anaesthesiol Scand 1985;29:515–9.

138. McNicol LR. Lower limb blocks for children—lateral cutaneous and femoral nerve blocks for postoperative pain relief in paediatric practice. Anaesthesia 1986;41:27–31.

139. Brown TCK, Dickens DRV. A new approach to lateral cutaneous nerve of thigh block. Anaesth Intensive Care 1986;14:126–7.

140. Chayen D, Nathan H, Chayen M. The psoas compartment block. Anesthesiology 1976;45:95–9.

141. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children—comparison of two procedures in 50 patients. Anesth Analg 1988;67:750–8.

142. Winnie AP, Ramamurthy S, Durrani Z, Radonjic R. Plexus blocks for lower extremity surgery. New answers to old problems. Anesthesiol Rev 1974;1:11–6.

143. Winnie AP, Ramamurthy S, Durrani Z. The inguinal paravascular technic of lumbar plexus anesthesia: the "3-in-1" block. Anesth Analg 1973;52:989–96.

144. Dalens B. Distal conduction blocks. In Ref 119, in press.

145. Touloukian RJ, Wugmeister M, Pickett LK, Hehre FW. Caudal anesthesia for neonatal anoperineal and rectal operations. Anesth Analg 1971;50:565–8.

146. Kay B. Caudal block for post-operative pain relief in children. Anaesthesia 1974;29:610–4.

147. Arthur DS. Caudal anaesthesia in neonates and infants. Anaesthesia 1980;35:1136–7.

148. Campbell MF. Caudal anesthesia in children. Am J Urol 1933;30:245–9.

149. Dawkins CJM. An analysis of the complications of extradural and caudal block. Anaesthesia 1969;24:554–63.

150. Busoni P, Andreuccetti T. The spread of caudal analgesia in children: a mathematical model. Anaesth Intensive Care 1986;14:140–4.

151. Spiegel P. Caudal anesthesia in pediatric surgery: a preliminary report. Anesth Analg 1962;41:218–21.

152. Bromage PR. Ageing and epidural dose requirements—segmental spread and predictability of epidural analgesia in youth and extreme age. Br J Anaesth 1969;41:1016–22.

153. Takasaki M, Dohi S, Kawabata Y, Takayashi T. Dosage of lidocaine for caudal anesthesia in infants and children. Anesthesiology 1977;47:527–9.

154. Hain WR. Anaesthetic doses for extradural anaesthesia in children. Br J Anaesth 1978;50:303.

155. Satoyoshi M, Kamiyama Y. Caudal anaesthesia for upper abdominal surgery in infants and children: a simple calculation of the volume of local anaesthetic. Acta Anaesthesiol Scand 1984;28:57–60.

156. Kapsten JE, Broadman LM, Hannallah RS, et al. Is there an optimum concentration of bupivacaine for caudal analgesia in outpatient surgery for children? Can Anaesth Soc J 1986;33:S114.

157. Warner MA, Kunkel SE, Offord KO, Atchison SR, Dawson B. The effect of age, epinephrine, and operative site on duration of caudal analgesia in pediatric patients. Anesth Analg 1987;66:995–8.

158. Ecoffey C, Desparmet J, Maury M, Berdeaux A, Giudicelli JF, Saint-Maurice C. Bupivacaine in children: pharmacokinetics following caudal anesthesia. Anesthesiology 1985;63:447–8.

159. Armitage EN. Regional anaesthesia in paediatrics. Clin Anaesthesiol 1985;3:553–68.

160. Melman E, Penuelas J, Marrufo J. Regional anesthesia in children. Anesth Analg 1975;54:387-90.

161. Ruston FG. Epidural anaesthesia in infants and children. Can Anaesth Soc J 1954;1:37-44.

162. Meignier M, Souron R, Le Neel JC. Postoperative dorsal epidural analgesia in the child with respiratory disabilities. Anesthesiology 1983;59:473-5.

163. Dalens B, Tanguy A, Haberer JP. Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children. Anesth Analg 1986;65:1069-73.

164. Ecoffey C, Dubousset AM, Samii K. Lumbar and thoracic epidural anesthesia for urologic and upper abdominal surgery in infants and children. Anesthesiology 1986;65:87-90.

165. Busoni P, Sarti A. Sacral intervertebral epidural block. Anesthesiology 1987;67:993-5.

166. Bromage PR. Complications and contraindications. In: Bromage PR, ed. Epidural analgesia. Philadelphia: WB Saunders, 1978:654-715.

167. Kane RE. Neurologic deficits following epidural or spinal anesthesia. Anesth Analg 1981;60:150-61.

168. Harrison PD. Paraplegia following epidural analgesia: case report. Anaesthesia 1975;30:778-82.

169. Bromage PR. Continuous epidural analgesia. In Ref 166, 215-57.

170. Scott DB, Wilson J. Insertion of epidural catheters. Anaesthesia 1983;38:1108-9.

171. Koch J, Nielsen JU. Rare misplacements of epidural catheters. Anesthesiology 1986;65:556-7.

172. Knill RL, Clement JL, Thompson WR. Epidural morphine causes delayed and prolonged ventilatory depression. Can Anaesth Soc J 1981;28:537-43.

173. Rawal N, Watwill M. Respiratory depression after epidural morphine—an experimental and clinical study. Anesth Analg 1984;63:8-14.

174. Attia J, Ecoffey C, Sandouk P, Gross JB, Samii K. Epidural morphine in children: pharmacokinetics and CO_2 sensitivity. Anesthesiology 1986;65:590-4.

175. Gleason CA, Martin RJ, Anderson JV, Waldemar AC, Sanniti KJ, Fanaroff AA. Optimal position for a spinal tap in preterm infants. Pediatrics 1983;71:31-5.

176. Weisman LE, Merenstein GB, Steenbarger JR. The effect of lumbar puncture position in sick neonates. Am J Dis Child 1983;137:107-9.

177. Armstrong IR, Littlewood DG, Chambers WA. Spinal anesthesia with tetracaine—effect of added vasoconstrictors. Anesth Analg 1983;62:793-5.

178. Caldwell C, Nielsen C, Baltz T, Taylor P, Helton B, Butler P. Comparison of high-dose epinephrine and phenylephrine in spinal anesthesia with tetracaine. Anesthesiology 1985;62: 804-7.

179. Mahe V, Ecoffey C. Spinal anesthesia with isobaric bupivacaine in infants. Anesthesiology 1988;68:601-3.

180. Shelly MP, Park GR. Intercostal nerve blockade for children. Anaesthesia 1987;42:541-4.

181. Moore DC, Mather LE, Bridenbaugh PO, et al. Arterial and venous plasma levels of bupivacaine following epidural and bilateral intercostal nerve blocks. Anesthesiology 1976;45:39-45.

182. Smith BAC, Jones SEF. Analgesia after herniotomy in paediatric day unit. Br Med J 1982;285:1466.

183. Markham SJ, Tomlinson J, Hain WR. Ilioinguinal nerve block in children—a comparison with caudal block for intra and postoperative analgesia. Anaesthesia 1986;41:1098-103.

184. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve block for control of post-orchiopexy pain in pediatric ambulatory surgery. Anesthesiology 1987;66:832-4.

185. Schulman J, Ben-Hur N, Neuman Z. Surgical complications of circumcision. Am J Dis Child 1964;107:149-54.

186. Martin LVH. Postoperative analgesia after circumcision in children. Br J Anaesth 1982;54:1263-6.

187. Vater M, Vandless J. Caudal or dorsal nerve block?—a comparison of two local anaesthetic techniques for postoperative analgesia following day-case circumcision. Acta Anaesthesiol Scand 1985;29:175-9.

188. Tree-Trakarn T, Pirayavaraporn S. Postoperative pain relief for circumcision in children: comparison among morphine, nerve block, and topical analgesia. Anesthesiology 1985;62: 519-22.

189. Tree-Trakarn T, Pirayavaraporn S, Lertakyamanee J. Topical analgesia for relief of post-circumcision pain. Anesthesiology 1987;67:395-9.

190. Broadman LM, Hannallah RS, Belman AB, Elder PT, Ruttimari U, Epstein BS. Post-circumcision analgesia—a prospective evaluation of subcutaneous ring block of the penis. Anesthesiology 1987;67:399-402.

191. Soliman MG, Tremblay NA. Nerve block of the penis for postoperative pain relief in children. Anesth Analg 1978;57: 495-8.

192. Yeoman PM, Cooke R, Hain WR. Penile block for circumcision? A comparison with caudal blockade. Anaesthesia 1983; 38:862-6.

193. Lau JTK. Penile block for pain relief after circumcision in children—a randomized prospective trial. Am J Surg 1984; 147:797-9.

194. Sara CA, Lowry CJ. A complication of circumcision and dorsal nerve block of the penis. Anaesth Intensive Care 1984;13:79-85.

195. Dalens B. Penile blocks. In Ref 119, in press.

Technical Communication

The Influence of Electrical Variables on Analgesia Produced by Low Current Transcranial Electrostimulation of Rats

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WILSON OB, HAMILTON RF, WARNER RL, JOHNSTON CM, deFRIECE R, HARTER L, SCHWEITZER C, TALAVERRA J, HYMEL CM, SKOLNICK MH. The influence of electrical variables on analgesia produced by low current transcranial electrostimulation of rats. Anesth Analg 1989;68:673–81.

Pulsed low current transcranial electrostimulation (TE) has been shown to induce analgesia in rats as measured by the wet tail flick test. This study investigates the effect of varying stimulus frequency, pulse width, charge balance and polarity, as well as the influence of electrode placement and time of day at which stimulus occurred.

A biphasic, charge balanced waveform with a first phase duration of 2 msec, current 10 μA and repetition rate 10 Hz was found to induce maximum tail flick latency changes. The effects of morning or nighttime stimulation were statistically indistinguishable, as were the differences between monophasic and biphasic stimulation. Analgesia was maximized when a positive first phase was delivered into the right ears of the rats, but monolateral stimulation with both electrodes on either the left or the right ear produced no measurable effect.

Examination of TE responses in sham and stimulated populations reveals normal response distributions with the stimulated group skewed toward a positive effect.

Key Words: ANESTHETIC TECHNIQUES—ELECTRONARCOSIS.

Several recent studies have presented evidence that low current transcranial electrostimulation (TE) can produce naloxone-reversible analgesia in rats (1–4). There are also indications that TE reduces the severity of opiate withdrawal syndrome in rats (3,4) and modulates the activity of single neurons in the rat brain (5–9). Despite significant differences between the electrical waveforms used in these studies and other published work, most notably with regard to stimulus current, the results are consistent with a large body of literature from the fields of electrostimulation and electroacupuncture in animals and hu-

mans (10–15). A more detailed comparison between the characteristics of TE and other similar forms of stimulation-induced analgesia is provided in Table 1 of a previous study (1).

As is the case with many other forms of electrostimulation, the analgesia induced by TE is mild and varies from subject to subject and from application to application. Nonetheless, the effects of varying stimulation characteristics can be quantified with use of the wet tail flick test, and this noxious response model forms the basis of a previous investigation of TE (1). The most striking finding presented in the study (1), and supported by a study of the effect of TE on acute morphine withdrawal in rats (4), is that there is only a narrow range of currents around $10 \mu A$ at which analgesia can be induced. Analgesia first appears after approximately 20 minutes of stimulation and intensifies for nearly 45 minutes after stimulation ends. The maximum effect is achieved after a
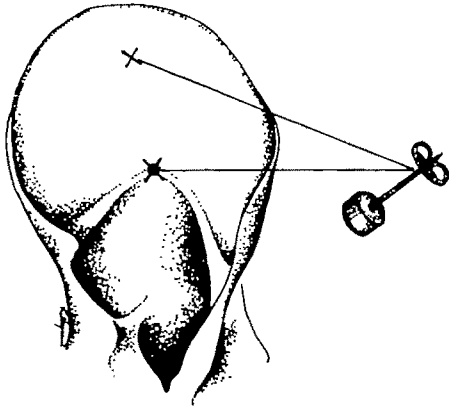
Figure 1. Sketch of a rat ear showing the sites of electrode placement. For Experiments 1-4, the standard site (solid circle) was used with one electrode placed on each ear. In Experiment 5, monolateral stimulation with two electrodes on either the left or the right ear was tested using electrode configuration (X). The stud shown in the illustration is not drawn to scale.

stimulus session lasting about 30 minutes, but this can be abolished by administration of opioid antagonist naloxone. Analgesia persists for 3 or more hours, and there is no evidence that tolerance to TE develops during five consecutive daily applications.

Although the mechanism of TE analgesia remains unclear, it is known that the effect is reversed by the opioid antagonist naloxone (1) and potentiated by the enkephalinase inhibitors acetorphan and thiorphan (16). It has also been found that the serotonin formation inhibitor pCPA reverses TE analgesia but that the effect is restored by subsequent administration of the serotonin precursor 5HTP (17). These findings are consistent with the hypothesis that opioid and serotonergic components of a pain modulating system are activated. Further support is provided by deep brain single cell recordings, performed on anesthetized rats, which indicate that the electrophysiological changes induced by TE are of the same magnitude as those induced by focal deep brain stimulation occurring in nuclei known to be involved in pain modulation (5-9). However, the fact that small TE currents are applied far from these brain nuclei leaves open the question of how and where electrical energy is transduced into electrophysiological and neurochemical activity.

One of the first steps in resolving this question is to determine whether changes in the electrical waveform influence TE-induced analgesia, and, if so, what waveform characteristics maximize the analgesia. This study extends earlier work using previously reported methodology (1) and investigates the effect of pulse width, frequency, polarity and charge balance on tail flick latency (TFL) changes in naive young male Sprague-Dawley rats. Because the endogenous opioid neurotransmitter systems are affected

by the 24-hour circadian rhythm (18,19), the effects of morning and nighttime TE are also tested.

Earlier work (1) indicates that the likelihood of a given rat responding to TE in any one trial is statistically independent of its responses in previous trials. This study presents an analysis of TFL changes in a large control group of rats and also in a group stimulated with the optimum electrical waveform. The result is a comprehensive picture of the statistical nature of TE analgesia.

Previous studies indicate that electro-analgesia may be produced by the action of stimulating currents directly on nerves or nerve pathways near the stimulation site (20), implying the possibility of a similar mechanism for TE. On the other hand, it is also possible that the stimulus currents may directly influence (presently unknown) brain regions by a volume conduction mechanism (21). As a first step towards resolving this question, and following examples from human clinical practice reviewed by Smith (10), attempts were made to induce analgesia by means of monolateral stimulation with both electrodes on either the left or the right ear.

Methods

Subjects. Male Sprague-Dawley rats (N = 189) weighing between 180 and 210 g at the time of electrostimulation were used. The animals were housed in groups of four with ad lib food and water and a 12:12 hour alternating light/dark cycle. All animals were naive in the sense that they had no previous experience with TE; however, a day before each experiment, the subjects were placed in restraints for 1 hour to acclimate them to the experimental conditions.

Electrode placement. Animals were anesthetized by injection of 450 mg/kg of body weight of chloral hydrate, i.p. For Experiments 1-5, gold plated stainless steel electrodes (cosmeticians' ear piercing studs) were inserted bilaterally into the pinnae at the apex of the antihelix (Fig. 1). This site was chosen because it resulted in a relatively low ear to ear impedance of 8.0 ± 0.4 KΩ, (N = 26), as reported previously (1). For the monolateral stimulation experiments, two studs were inserted into either the left or the right ear only (see Fig. 1). Each rat was allowed at least 48 hours to recover after electrode implantation.

Transcranial electrostimulation (TE). A computer controlled stimulator was used to produce a continuous series of biphasic, charge balanced, rectangular pulses which, unless otherwise specified, had a rep-
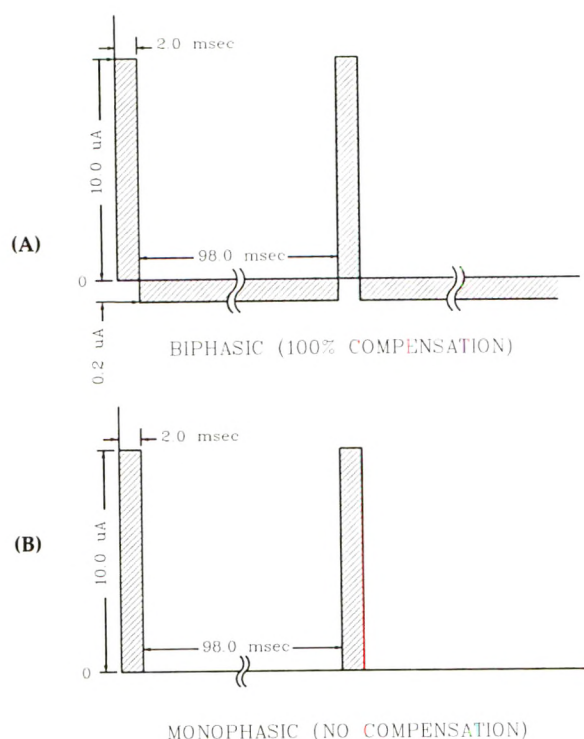
Figure 2. Diagrammatic illustration of TE waveforms. (a) A biphasic charge balanced waveform, with positive first phase and negative, low amplitude, long duration second phase. (b) A monophasic non-charge balanced waveform, as used in Experiment 3.

etition rate of 10 Hz, first phase amplitude 10 μA, and first phase duration 2 msec. The second phase duration was approximately equal to the interval between consecutive first phases, and the amplitude such that the net charge delivered in any cycle was 0. A typical pulse is diagramed in Figure 2.

In the experiments reported in this study, an essentially constant ($\pm 2\%$) stimulus current was maintained by connecting the constant voltage waveform generator in series with a 200 KΩ resistor. Newer stimulators now in use differ from this configuration in the implementation of a digital sensing and feedback system that actively maintains a constant stimulus current.

Fifteen minutes before stimulation, the rats were placed in adjustable cylindrical plastic restrainers to which they had previously been acclimated. Leads were connected to the electrodes with the positive lead (that delivering a positive first phase) attached to the animals' right ears. Each experiment included a "sham control group" consisting of rats that were implanted, restrained, and connected as previously mentioned, but that did not receive any electrical stimulation.

All observations were carried out by operators who were blind to the stimulus parameters and to which animals received stimulation. Care was taken

to exclude systematic influences on the data arising from stimulation at different times of day by stimulating and testing equal numbers of animals from each stimulus or sham group in every stimulation session.

Measurement of analgesia. Analgesia was assessed using the wet tail flick method (22,23). Although there are numerous analgesic models reported in the literature, including several versions of the tail flick test using wet heat, dry heat and pressure (among others), there is no consensus as to which method is best in any given situation (24,25). TE experiments conducted in our laboratory indicate that a pressure measure is more sensitive than the wet tail flick (17), and a dry heat measure also gives good results. However, for consistency with previous work, this study uses only the wet heat test.

Immediately preceding and after electrostimulation, the distal 2.5 cm of each rat's tail was immersed in water at 50°C. The time in seconds measured with a stopwatch from submergence to the first flicking response was taken as the tail flick latency. If a rat did not respond within 20 seconds, its tail was removed from the water to prevent tissue damage. During this study, no rat left its tail immersed for 20 seconds. Examination of the tails after repeated tail flick tests revealed no tissue damage. Four successive latencies were determined during both the pre- and post-test. In each case, the first measurement was discarded and the last three were averaged to yield pre- and post-stimulus scores. Each rat's analgesia rating was its mean post-test latency minus its mean pre-test latency.

Statistical analysis. All analyses of variance were conducted using SYSTAT, a commercially available software package (26). Two other tests were used in the analysis of results: Tukey's Honestly Significant Difference (HSD) test and Dunnett's Test for Multiple Comparison to a Single Control Group (27).

Tukey's HSD is a conservative one tailed post hoc test designed to avoid errors occurring in multiple comparisons of experimental groups. This test establishes a critical range between group means that allows multiple comparisons between any two groups in the experimental design. It is available in the SYSTAT package.

Dunnett's test is a one tailed post hoc statistical measure designed for comparing a single group with multiple other groups. It is not available on the SYSTAT package and was performed by hand.

Ethical statement. All experimental procedures were approved by the Animal Experiment Council of

the University of Texas Health Science Center and are in compliance with the proposals of the Committee for Research and Ethical Issues of IASP (28).

Procedure

Experiment 1 tested the analgesic effects of different stimulus pulse widths in 63 rats not previously exposed to TE that were randomly assigned to seven groups of 9 rats each. These groups had 30 minutes of 10 μA, 10 Hz stimulation with, respectively, 0 (sham), 0.1, 0.5, 1, 2, 4, and 8 msec first phase pulse widths. As in all the following experiments, tail flick latencies (TFLs) were determined before and after stimulus by an operator who was blind to the stimulus parameters, and the time difference in seconds determined the animals' analgesia scores.

Experiment 2 tested the analgesic effects of different stimulus frequencies in 63 rats randomly assigned to 7 groups of 9 rats each. These groups had 30 minutes of 10 μA, 2 msec pulse width stimulation at 0 (sham), 5, 5.7, 10.0, 15, 20, and 50 Hz.

Experiment 3 tested the necessity of using a charge balanced stimulus waveform in 27 rats randomly assigned to 3 groups of 9 rats each. These groups had 30 minutes of stimulus with, respectively, no stimulus waveform (sham); 10 Hz, 2 msec, 10 μA stimulation with a charge balanced waveform; or 10 Hz, 2 msec, 10 μA stimulation with a monophasic (non-charge-balanced) waveform as illustrated in Figure 2.

Experiment 4 tested the effect of stimulus polarity on the analgesia produced by TE in 15 rats tested three times in a blind, triple crossover design with 30-minute stimulus sessions. Each rat received one session of sham stimulation; one of 10 Hz, 2 msec, 10 μA charge balanced TE with standard polarity (positive lead on the right ear); and once of 10 Hz, 2 msec, 10 μA TE with reversed polarity (positive lead on the left ear). TFL analgesia scores in this experiment were determined in all animals before and after each session. Statistically weak results lead to a repeat of the experiment using a further 12 subjects in the same triple crossover design. The experiments were analyzed separately as noted in the Discussion.

Experiment 5 examined the possibility of circadian influences on the TE analgesic response in 17 rats under four conditions: light cycle, no TE; dark cycle, no TE; light cycle with TE; and dark cycle with TE. A repeated measures, crossover design was employed so that half of the rats received their first stimulation in the light cycle, and half received it in the dark cycle. Every rat thus participated in every condition. Simulated darkness was achieved in the dark cycle by using low wattage, red filtered lighting that allowed
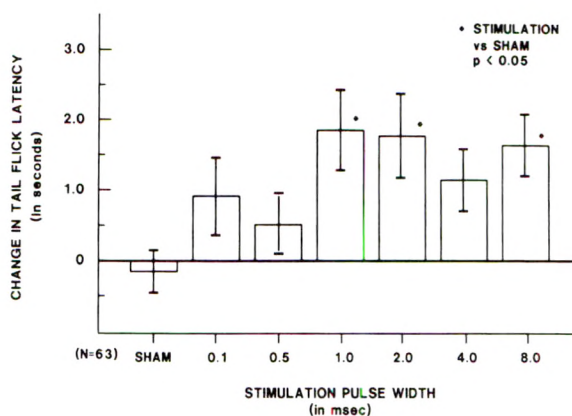
Figure 3. Analgesic effects of different electrostimulation pulse widths. Sixty-three rats were randomly assigned to seven groups of nine. Each group received 30 minutes of 10 μA, 10 Hz stimulation with 0 (sham), 0.1, 0.5, 1, 2, 4, or 8 msec pulse widths. The 1, 2, and 8 msec groups were shown by Dunnett's test to have significantly higher analgesia scores than the sham controls, $P < 0.05$.

the experimenters to conduct the experiment. The experiments were performed 5 hours $\pm$ 30 minutes into the respective cycles. Each stimulated rat received 30 minutes of 10 Hz, 2 msec, 10 μA charge balanced TE, and TFL analgesia scores were determined in the usual way.

Experiment 6 investigated the efficacy of several electrode positioning schemes in 36 rats randomly assigned to three groups of 12 rats each. One group had one electrode in each ear; the other two groups had two electrodes in either the left or the right ear as illustrated in Figure 1. Each animal had 30 minutes of 10 Hz, 2 msec, 10 μA charge balanced TE. TFL analgesia scores were determined in the usual way under blind conditions.

Results

The results of Experiment 1, varying waveform pulse width, are illustrated in Figure 3. A one-way analysis of variance indicates a significant effect for pulse width on the change in tail flick latency, $F(6,56) = 2.283$, $P < 0.05$. According to Dunnett's test for multiple comparisons with a single control, three groups (1, 2, and 8-msec pulse widths) differed significantly from sham in post hoc comparison, $P < 0.05$. Although the 2-msec group showed the greatest overall degree of analgesia, the difference between this and the 1 or 8-msec groups was not statistically significant.

The results of Experiment 2, varying frequency of electrostimulation, are shown in Figure 4. The 10 Hz group showed the greatest increase, 45%, in tail flick latency (2.28 $\pm$ 0.61 sec). A one-way analysis of
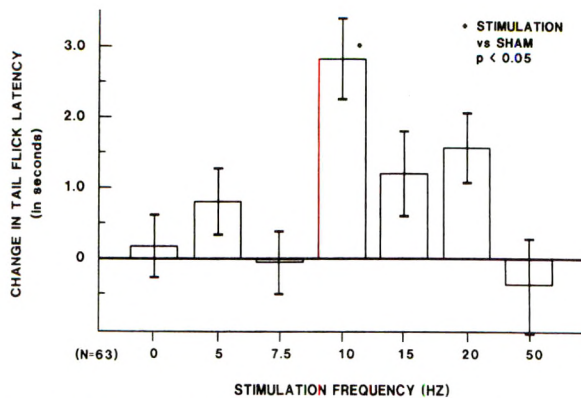
Figure 4. Analgesic effects of different electrostimulation frequencies. Sixty-three rats were randomly assigned to seven groups of nine. Each group received 30 minutes of 10 μA, 2 msec stimulation at 0 (sham), 5, 7.5, 10, 15, 20, or 50 Hz. According to Tukey's HSD test, the 10 Hz stimulated animals had significantly higher analgesia scores than the sham group, $P < 0.05$.
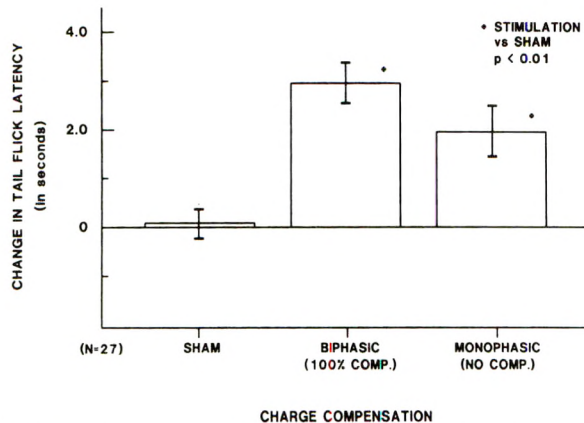
Figure 5. Analgesic effects of biphasic versus monophasic stimulus waveforms. Twenty-seven rats were randomly assigned to three groups of nine. Each group received 30 minutes of sham (no stimulation), charge-balanced biphasic, or monophasic 10 Hz, 10 μA, 2 msec TE. According to Tukey's HSD test, both stimulated groups showed significantly higher analgesia scores than the sham controls, $P < 0.01$.

Figure 6. Analgesic effects of stimulus polarity. (a) 15 rats were stimulated in a blind triple crossover experiment for 30 minutes with each of sham, standard polarity TE, and reverse polarity 10 Hz, 2 msec, 10 μA TE. Tukey's HSD test reveals that the standard polarity group, but not the reverse polarity group, showed greater analgesia than the sham animals, $P < 0.05$. (b) A further 12 rats were stimulated in the same experimental design. Tukey's HSD test indicates that the standard polarity group differed from both the reverse polarity group, $P < 0.05$, and from the sham group, $P < 0.01$.

variance reveals a significant effect of electrostimulation frequency on the change in tail flick latency, $F(6,56) = 4.012$, $P < 0.002$. Post hoc comparisons using Tukey's HSD test show that only the 10 Hz group differed significantly from the sham controls, $P < 0.05$.

The results of Experiment 3, effect of charge balance on changes in tail flick latency, are illustrated in Figure 5. The greatest increase in latency (2.95 ± 0.43 sec), which represents a 49% increase in response time, occurred in the rats given charge balanced stimulation. A one-way analysis of variance shows a significant effect for both mono- and bipolar stimulation on the change in tail flick latency, $F(2,24) = 13.703$, $P < 0.001$. Post hoc comparisons using Tukey's HSD test indicate that both stimulus groups,

regardless of charge compensation, were significantly different from sham, $P < 0.01$. Although the biphasically stimulated group showed a TFL increase averaging 1 sec more than the monophasically stimulated group, this difference was not statistically significant.

The results of Experiment 4, two successive tests of varying stimulus polarity, are illustrated in Figures 6a and b. In the first experiment, with 15 animals, a one-way analysis of variance indicates a significant effect of stimulation, $F(2,28) = 4.579$, $P < 0.02$. Comparison with Tukey's HSD test revealed that the group receiving positive stimulation on the right ear had a significant increase in TFL compared to sham, $P < 0.05$. However, the reverse polarity group did not differ significantly with respect to either positive treatment or sham groups. The experiment was repeated with a further 12 rats (see Discussion). In the second experiment, one-way analysis of variance also indicated a significant effect of stimulation, $F(2,22) = 7.546$, $P < 0.003$. Comparison with Tukey's HSD test
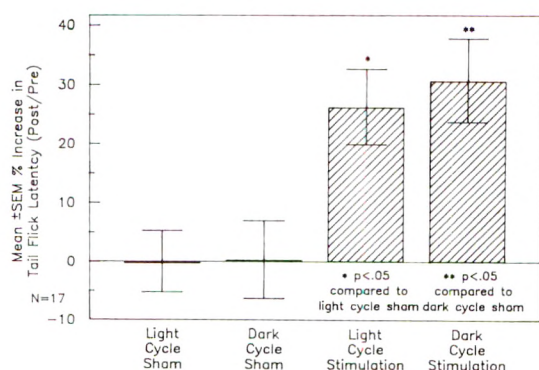
Figure 7. Effect of circadian rhythm. Seventeen rats were used in a four-way crossover design to test the effect of circadian rhythm on TE induced analgesia given 5 hours into either the light or the dark cycle for the animals. Every rat participated in each of four conditions: light cycle, no TE; dark cycle, no TE; light cycle with TE; and dark cycle with TE. When stimulated, each rat received 30 minutes of 10 Hz, 2 msec, 10 μA TE. According to Tukey's HSD test, there was no significant difference between the analgesia induced in light and dark stimulated rats, $F(1,16) = 0.22$, n.s.
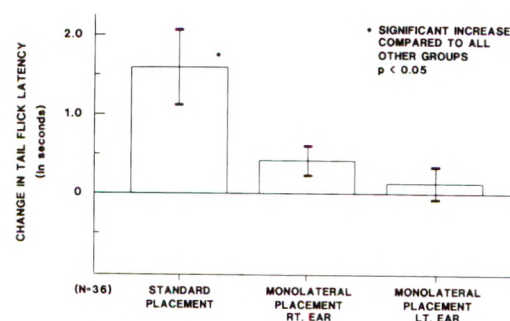
Figure 8. Analgesic effects of electrode placement. Twelve rats were implanted with electrodes in the standard position; 12 with two electrodes in the left ear; and 12 with two electrodes in the right ear (see Figure 1). Each group received 30 minutes of 10 Hz, 2 msec, 10 μA TE. According to Tukey's HSD test, the standard placement group showed significantly greater analgesia than either the left monolateral group or the right monolateral group $P < 0.05$.

revealed a significant difference between positive and sham groups, $P < 0.01$, and also between positive and reverse polarity groups, $P < 0.05$. Analysis of the combined results from both groups, N = 27, indicates a highly significant difference between positive polarity and sham, $P < 0.01$, and between positive polarity and reverse polarity, $P < 0.01$. In neither of the two polarity experiments, nor in the combined results, did the reverse polarity group differ significantly from sham.

The results of Experiment 5, which examined the influence of circadian rhythm on TE-produced analgesia are illustrated in Figure 7. A two-way, repeated measures analysis of variance indicates a significant main effect of stimulation, $F(1,16) = 19.64, P < 0.001$. There was no main effect for cycle (dark versus light), $F(1,16) = 0.22$, n.s. Likewise, there was no significant interaction, $F(1,16) = 0.082$, n.s. In post hoc comparisons using Tukey's HSD test, both stimulus groups showed a significant increase over their respective sham group, $P < 0.05$.

The result of Experiment 6, which tested the effect of various electrode placements, is shown in Figure 8. A one-way analysis of variance indicates a significant effect of electrode placement, $F(2,33) = 5.945, P < 0.01$. Post hoc comparison using Tukey's HSD test indicates a significant difference with the group receiving standard electrode placement showing an increased TFL compared with either of the monolateral stimulation groups, $P < 0.05$.

Discussion

Experiment 1, which shows that 1, 2, and 8 msec pulsewidth TE are all capable of inducing analgesia

when combined with previously reported findings (1) that demonstrate that 0.1 msec stimulation is also effective, indicates that with these rectangular stimulus waveforms, pulsewidth is not a critical TE parameter. Similarly, Experiment 2 indicates that whereas 10 Hz charge balanced TE induced maximum analgesia, there was no clear optimum stimulus frequency, and no strong reason to favor biphasic stimulation over monophasic. Nonetheless, there does appear to be some degree of frequency dependence to the TE effect because the results at 7.5 Hz and 50 Hz or higher indicated little analgesia. The reason for this dependence is not known but is consistent with other published reports (29).

On the basis of Experiment 3, the only reason for selecting a charge balanced waveform is to reduce polarization effects at the highly capacitive electrode/tissue interface (30). However, it should be noted that in clinical trials of TE as an aid to smoking cessation (31), the incidence of reported headaches was higher with monophasic stimulation than that with a charge balanced waveform. Experiments 1–3 are in general agreement with the references listed in Table 1 of the previous study (1) in which positive results from a wide range of transcranially applied stimulus waveforms are reported.

The purpose of Experiment 4 was to determine whether stimulus polarity has any effect on TE analgesia. On examination of the original results from a triple crossover design with 15 animals, no definitive conclusion could be reached, and it was decided to repeat the experiment. The only rats available for this had been intended for a different study altogether and differed from the first group in that they had been subjected to daily handling and acclimatization to the restraint for one week before the experiment. However, the results of this repeat experiment were more definitive, indicating significant differences between the positive stimulus group and both sham

and reverse polarity groups. Strictly speaking, differences in handling the two groups of rats preclude a combined statistical analysis, but if such an analysis is performed, the same conclusion as for the repeated experiment is obtained with a higher significance level.

The differences between the first and second iterations of this experiment are illustrative of a general problem encountered with measuring TE analgesia. Owing to the weakness of the effect, uncontrollable influences such as excessive noise or activity in the animal care quarters can obscure differences between treatment and sham groups. This effect was originally noticed at a time when the vivarium was under renovation, and daily jackhammering stressed the animals to an extraordinary degree. TE amelioration of opiate withdrawal syndrome is a much stronger effect and appears to be largely immune to such disturbances (4).

The result of Experiment 4 is somewhat puzzling, seeming to indicate that greater analgesia is achieved if a positive current, or in the case of biphasic stimulation, a positive first phase, is delivered into the subject's right ears. However, this would imply some kind of asymmetry in the underlying structures, presumably neural, on which the stimulus current acts. At present there is no indication as to the origin or nature of such asymmetry, or to possible differences between left-pawed and right-pawed animals, and these topics remain the subject of ongoing research.

In analogy with findings of research into the mechanisms of TENS and acupuncture (20,32), it was initially hypothesized that TE analgesia results from excitation of nerves in the pinnae near the electrodes. However, Experiment 6, in combination with other previous work (1), points to the conclusion that a transcranial current path is necessary for TE to be effective. This is surprising because at first glance, the very low currents used in TE do not appear capable of directly affecting neurons in the central nervous system, and they are well below the level required to induce a startle or flinch response (4). Nonetheless, at the single cell level, inhibition of noxious responses occurs within a minute of starting TE (5–9). Although some work has addressed the action of small currents on the brain (21), the possible central action of TE remains difficult to explain.

Involvement of endogenous opioids in TE analgesia, and the known circadian variations in such neurotransmitter systems (18,19), raises the question of possible circadian effects of TE analgesia. Comparison of morning TE with stimulation given 12 hours later in the "dark" cycle revealed no circadian effects. Although it is possible that variations do occur at
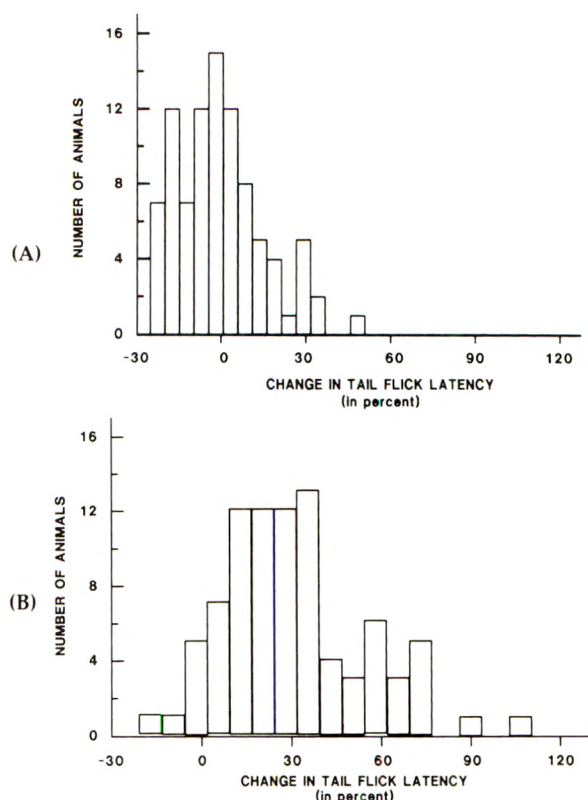
Figure 9. TFL response histograms. (a) The distribution of percentage TFL score changes between pre- and post-stimulation in sham rats, N = 91. (b) The distribution of percentage TFL score changes between pre- and post-stimulation in rats stimulated with 10 Hz, 2 msec, 10 μA TE for 30 minutes, N = 86.

times not tested in Experiment 5 (e.g., late in the afternoon), this result does not give any indication of circadian variations.

A combination of results from this study and previous work (1) makes possible a more detailed analysis of the analgesic response to TE in a large group of subjects. Figure 9a is a histogram showing the distribution of percentage changes in post- minus pre-stimulus TFL scores for sham rats with a mean increase of 3.30% $\pm$ 1.78%, N = 90. Figure 9b shows the changes for rats stimulated with 0.1 msec, 10 Hz, 10 μA, charge balanced TE of standard polarity for 30 minutes, with a mean increase of 32.9% $\pm$ 2.6%, N = 86. Statistical comparison of these distributions reveals a highly significant difference, t(174) = 9.329, $P < 0.0005$. Both curves show central tendencies probability plots that reflect normal distributions. The stimulated group distribution is skewed toward a positive analgesic response but contains a significant population of non-responding subjects.

The response trends of such subject groups over repeated sessions has been discussed previously (1), and it has been shown that individual responses in a given trial are statistically independent of those in previous or subsequent trials. Interestingly enough,

this is in contrast to recently reported results with acupuncture-like electrostimulation in which the experience of subject animals strongly influences their subsequent responses to stimulation (33).

Figures 9a and 9b highlight a fundamental difficulty encountered with optimizing the TE stimulus waveform for maximum analgesia: the weakness of the effect, and its variability from subject to subject, obscure peaks in the response curves (notably Figures 3 and 4), if indeed such peaks exist. One possible approach to improving matters is to use a different measure of analgesia, such as abdominal writhe, tail pressure or dry heat tail flick, which might provide greater sensitivity with less variability. Because TE analgesia is at least partly neurochemically mediated (1,17), another possibility is to seek a more powerful analgesic effect by co-administering neurotransmitter precursors, degradation inhibitors, or competitive system antagonists. This approach is currently the subject of intensive ongoing research (16). The alternative of using a different measure of TE efficacy, such as the attenuation of opiate withdrawal symptoms in morphine addicted rats, which has been shown to be a remarkably strong effect (4), would result in a much more laborious experimental procedure.

On the basis of the evidence to date, it appears that 30 minutes of TE with an amplitude of 10 μA, frequency near 10 Hz, and a pulse width of around 2 msec induced maximum analgesia in rats. The stimulus waveform should be applied transcranially with the positive lead on the subjects' right ears. Biphasic stimulation may prove to be slightly more effective than monophasic. Other work in progress aims to determine the locus of action of TE currents and will attempt to find correlates to the analgesia, particularly blood and CSF biochemical changes and deep brain electrophysiological indicators.

Although the analgesia induced by TE is mild, ongoing work indicates that the effect may well be increased by various promoter substances, including enkephalinase inhibitors (16) and possibly several neurotransmitter precursors. Even if TE-induced analgesia cannot be boosted by such means to clinically useful levels, animal studies suggest that the process may have promise as an aid to narcotic drug detoxification (4). As an additional benefit, it appears likely that a greater understanding of the interaction between electric current and the nervous system may emerge from this research.

References

1. Skolnick M, Wilson O, Hamilton RF, Collard CD, Hudson-Howard L, Hymel C. Low current electrostimulation produces naloxone-reversible analgesia in rats. Stereotactic Funct Neurosurg (formerly Appl. Neurophysiol). 1989:3 (in press).

2. Skolnick M, Collard CD, Hamilton R, Hudson-Howard L, Hymel C, Wilson O. Transcranial electrostimulation increases tail flick latencies after nociceptive challenge. Proc Soc Neurosci 1987;13:1304.

3. Murray JB, Schweitzer FC, Locke GG, Sweet LA, Cron SG, Malin DH. Transcranial auricular electrostimulation (TCET): naloxone reversible attenuation of pain sensitivity and opiate abstinence syndrome. Proc Soc Neurosci 1987;13:1304.

4. Malin DH, Murray JB, Crucian GP, Schweitzer FC, Cook RE, Skolnick M. Auricular transcranial electrostimulation: naloxone reversible attenuation of opiate abstinence syndrome and pain sensitivity. Biol Psychiatry 1988;24:886–90.

5. Qiao JT, Skolnick M, Dafny N. Dorsal raphe and external electrical stimulation modulates noxious input to single neurons in nucleus parafascicularis thalami. Brain Res Comm 1988;21:671–6.

6. Dafny N, Dong WQ, Qiao JT, Skolnick M. Habenular noxious responses are modulated by dorsal raphe, lateral hypothalamus and external electrical stimulation. J FASEB 1988;2:A1071.

7. Skolnick M, Dong WQ, Qiao JT, Dafny N. Descending and ascending pathways modulate noxious responses of medial thalamic neurons. J FASEB 1988;2:A1071.

8. Dong WQ, Skolnick M, Dafny N. Lateral hypothalamic noxious responses are modulated by habenular, dorsal raphe and external electrical stimulation. J FASEB 1988;2:A1071.

9. Dong WQ, Skolnick M, Dafny N. Effects of dorsal raphe, habenula and external stimulation on septal neurons in the rat. Proc Soc Neurosci 1988;14:855.

10. Smith RB. Cranial Electrotherapy Stimulation. In: Neural Stimulation, Vol. II. Myklebust JB, Cusick JF, Sances A, Larson SJ. eds. Boca Raton, Florida: CRC Press, 1985;129–50.

11. Sances A, Larson SJ. Electroanesthesia: Biomedical and Biophysical Studies. New York: Academic Press, 1975.

12. Xiangtong Z. Research on Acupuncture, Moxibustion, and Acupuncture Anesthesia. New York: Science Press, 1986.

13. Liu X, Zhu B, Zhang S. Relationship between electroacupuncture analgesia and descending pain inhibitory mechanism of nucleus raphe magnus. Pain 1986;24:383–96.

14. Capel ID, Pinnock MH, Williams DC. The influence of different electrical stimulation in hexobarbital induced loss of righting reflex in rats. Int J Acupunct Electrotherap Res 1982;7:16–26.

15. Pert A, Dionne R, Ng L, Bragin E, Moody TW, Pert CB. Alterations in rat central nervous system endorphins following transauricular electroacupuncture. Brain Res 1981;224:83–93.

16. Lake JR, Hamilton RF, Skolnick M, Malin DH, Enkephalinase inhibitor thiorphan potentiates analgesic effect of transcranial electrostimulation (TCES). Proc Soc Neurosci 1988;14:855.

17. Hudson-Howard L, Warner R, Johnston C, Skolnick M. Serotonin involvement in analgesia induced by transcranial electrostimulation. Proc Soc Neurosci 1988;14:855.

18. Frederickson, RCA, Burgin V, Edwards JD. Hyperalgesia induced by naloxone follows diurnal rhythm in responsivity to painful stimuli. Science 1977;198:756–8.

19. Przwlocki R, Lason W, Konacka AM, Gramsch C, Herz A, Reid LD. The opioid peptide dynorphin, circadian rhythms, and starvation. Science 1983;219:71–3.

20. Man PL, Chen CH. Acupuncture anesthesia—a new theory and clinical study. Curr Therapeutic Res 1972;14:390–4.

21. Lippold OCJ, Redfearn JWT. Mental changes resulting from the passage of small direct currents through the human brain. Brit J Psychiatry 1964;110:768–72.

22. Mitchell D, Hellon RF. Neuronal and behavioral response in rats during noxious stimulation of the tail. Proc R Soc (Lond) 1977;B197:169–94.

23. Sicuteri F, Franchi G, Michelacci S. Biochemical mechanisms of ischemic pain. Adv Neurol 1974;4:39–43.

24. Vyklicky L. Methods of testing pain mechanisms in animals. In: Testbook of Pain. Edinburgh: Churchill Livingstone, 1984: 178–85.

25. Dennis SG, Melzack R. Pain modulation by 5-hydroxytryptaminergic agents and morphine as measured by three pain tests. Exp Neurology 1980;69:260–70.

26. Wilkinson L. SYSTAT: The system for statistics. Evanson, IL: SYSTAT, Inc., 1986.

27. Zan JH. Biostatistical Analysis, 2nd ed. Englewood Cliffs, NJ: Prentice-Hall, 1984.

28. Zimmermann M. Ethical guidelines for investigators of experimental pain in conscious animals. Pain 1983;16:109–10.

29. Chung S-H, Raymond SA, Lettvin JY. Multiple meaning in single visual units. Brain Behav Evol 1970;3:72–101.

30. Onaral B, Sun HH, Schwan HP. Electrical properties of bioelectrodes. IEEE Trans Biomed Eng 1984;31:827–32.

31. Skolnick M, Blacker M, Skolnick L, Langone J, Sands S, Smith D. Clinical tests of electrostimulation in the relief of chronic pain and smoking cessation. Phys Med Biol 1988;33:399.

32. Abram SE. Transcutaneous electrical nerve stimulation. In: Neutral Stimulation, Vol. II. Myklebust JB, Cusick JF, Sances A, Larson SJ, eds. Boca Raton, Florida: CRC Press, 1985:1–10.

33. Mayer DJ. Electro-acupuncture analgesia: evidence for endogenous opioid facilitatory and inhibitory effects. Phys Med Biol 1988;33:395.

Fifty-Seven Years Ago In

𝕬𝖓𝖊𝖘𝖙𝖍𝖊𝖘𝖎𝖆 & 𝕬𝖓𝖆𝖑𝖌𝖊𝖘𝖎𝖆

Fifty-seven years ago in Current Researches in Anesthesia and Analgesia: 1932;11:177–183. P. D. Woodbridge: Neothesin for Spinal and Regional Anesthesia: A Preliminary Clinical Report

This article introduces into clinical practice a new local anesthetic, neothesin, at a time when procaine had reigned supreme for 30 yr as the alpha and omega of local anesthetics. The pharmacology and systemic toxicity of neothesin (a.k.a. metycaine, monocaine, and eventually, NNR piperocaine) in experimental animals had been reported in the preceding 3 yr, as had its metabolism and systemic toxicity (see this journal 1931; 10:103 and the references it cites). The clinical use of neothesin for infiltration and field blocks had also been reported a year before this article appeared (e.g., W. R. Meeker: Surg Gynec Obstet 1930;50:997). But this is the first report of the use of a local anesthetic other than procaine for major regional anesthesia in humans. As such, the paper reflects the long search for a local anesthetic with a longer duration of action and with less systemic toxicity than procaine. Equally important, this paper also reflects the coming of age of chemical engineering in the pharmaceutical industry to the point where it became possible to synthesize compounds that had been predicted, on the basis of structure–activity relationships established as early as 1910, to be effective local anesthetics but for technical reasons were previously impossible to manufacture. The increased sophistication of pharmaceutical synthetic methods at this time is seen also in the subsequent introduction by other companies of two competing local anesthetics: dibucaine (originally percaine but later nupercaine) and tetracaine (pontocaine).

The author of this paper, Woodbridge, was a widely known and respected anesthetist at the Lahey Clinic in Boston. He later became even more widely known for his seminal paper defining and separating out the various different components that make up surgical anesthesia (Anesthesiology 1957;18:536). In this article Woodbridge reports that 120–320 mg neothesin in 4–6 mL CSF produced satisfactory spinal anesthesia in 42 of 43 patients. The one failure was attributed to use of barbotage rather than the Trendelenburg position to achieve the desired level of anesthesia. Nine of the 43 operations were intraabdominal. Anesthesia lasted about one and a half hours with neothesin, about 30 min longer than procaine. Surgeons had to move right along in those days. Woodbridge also used neothesin (0.5–1.0%) for caudal and/or transsacral blocks in five patients, for abdominal wall field blocks (cholecystectomy, gastrectomy, etc.) in seven patients, and for cervical plexus blocks (thyroidectomy, esophageal diverticulectomy) in two patients.

This article also reminds us how easy it was to introduce new drugs 50 yr ago. After this paper appeared, neothesin rapidly became a widely used local anesthetic. There was no need at that time for multicenter collaborative studies of thousands of patients and multimillion dollar expenditures to get approval of a new drug by a not-yet-existent Food and Drug Administration (FDA). More convenient, yes, but ultimately at a cost in terms of human morbidity and mortality, as attested to by the track record of many other drugs introduced with similar ease prior to the eventual establishment of the FDA.

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Clinical Reports

First Rib Palpation: A Safer, Easier Technique for Supraclavicular Brachial Plexus Block

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The supraclavicular approach to local anesthetic blockade of the brachial plexus offers several advantages over other approaches. It has a high success rate and rapid onset of action (1). Compared with the axillary approach, it provides more complete anesthesia of the plexus, particularly the axillary and musculocutaneous nerves, and does not require abduction of the arm to perform. The interscalene approach is complicated by a higher incidence of injection into epidural or subarachnoid spaces or into the vertebral artery. It also is relatively difficult to master (1).

The most significant problem that has prevented supraclavicular block from achieving widespread use has been pneumothorax, a complication that has a reported incidence of 0.6 to 5.0% (1). We describe a simple technique utilizing palpation of the first rib to improve the ease of supraclavicular brachial plexus block, which also should decrease the potential of lung injury.

Anatomy

The brachial plexus and the subclavian artery cross over the first rib deep to the clavicle at its midpoint (Fig. 1). The plexus, at this level, is enclosed in a compartment bordered by the anterior scalene muscle and its fascial extension anteriorly and by the first rib posteriorly (Fig. 2). More superiorly, the posterior

border of this compartment comprises the middle scalene muscle and its fascial extension. Distal to the first rib, the plexus is circumferentially enclosed by this fascial sheath. As the plexus crosses the first rib, it is most compact and has the least fascial subcompartmentalization as the three trunks unite to form the nerves of the plexus (1). The first rib, as it leaves the supraclavicular fossa, crosses under the clavicle where it can be reliably palpated.

Landmarks

With the patient lying supine, the landmarks are 1) the external jugular vein that descends down the neck to 2) the midpoint of the clavicle (Fig. 3) and, most importantly, 3) the first rib that is palpated between index and long fingers as they rest on the superior border of the clavicle (Fig. 4).

Procedure

With the first rib located between index and long fingers as described (see Landmarks), with use of an immobile needle technique, a 3.8 cm, 22-gauge, short-beveled needle is inserted into the skin directly between the fingertips, perpendicular to the skin in all planes (Fig. 5). As the needle is advanced, the "click" of the fascial sheath is felt, usually 1–2 cm deep to the skin. Local anesthetic may be injected at this point, or other techniques to confirm needle tip location within the neurovascular compartment may be employed. Paresthesias may be sought by fanning the needle along the plane between the fingertips. The artery may be contacted by the needle resulting in pulsations felt at the hub, or the artery may be punctured and the needle withdrawn until blood is
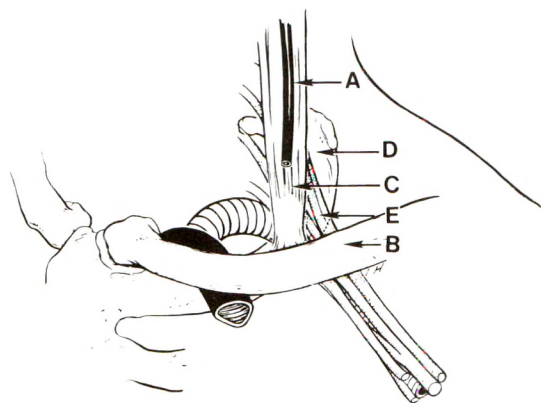
Figure 1. Anatomy of the brachial plexus. **A,** External jugular vein; **B,** Clavicle; **C,** Anterior scalene muscle; **D,** First rib; **E,** Brachial plexus.
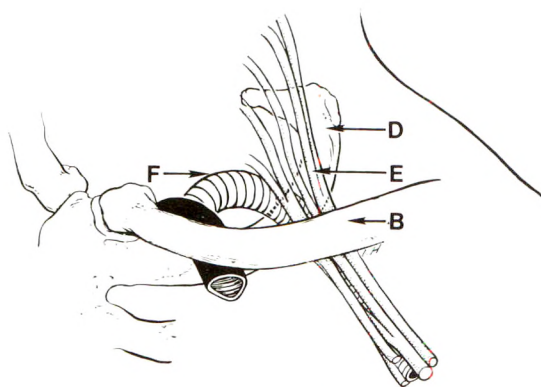
Figure 2. Anatomy of the brachial plexus with external jugular vein and anterior scalene muscle removed to better show the relationship of the brachial plexus to the first rib. **B,** Clavicle; **D,** First rib; **E,** Brachial plexus; **F,** Subclavian artery.

Figure 3. Landmarks for palpation of the first rib. **A,** External jugular vein; **B,** Midpoint of clavicle.

no longer aspirated. Alternatively, the needle can be advanced until the first rib is contacted (usually 3–4 cm deep to the skin) and then withdrawn one centimeter, at which point local anesthetic is injected. At the lateral aspect of the first rib, the plexus is bordered anteriorly by fascia, the first tissue plane deep to the skin, and posteriorly by the first rib. As long as local anesthetic is not deposited subcutaneously, it should be properly located in the neurovascular compartment.

Local anesthetic, 25–40 ml, may be injected to obtain surgical anesthesia of the brachial plexus. Anesthesia of the medial upper arm may then be achieved by injecting a subcutaneous wheal of local anesthetic in the axilla perpendicular to the brachial artery to block the intercostobrachial nerve (2).

Methods

Twenty-eight adult patients (15 male, 13 female; age 47 ± 9 years; weight 76 ± 12 kg) undergoing surgery

of the upper extremity were anesthetized with use of the described technique. Forty milliliters of 1.5% lidocaine with epinephrine 1/200,000 that was pH adjusted by the addition of sodium bicarbonate (1:10 ml of lidocaine) were injected into the neurovascular compartment. All of the various needle placement techniques described previously were employed: feeling for the "click" of the anterior fascial sheath ($n = 3$), paresthesia ($n = 16$), arterial pulsations felt through the needle ($n = 2$), arterial puncture ($n = 4$), and contacting the first rib with the needle ($n = 3$). The intercostobrachial nerve was anesthetized with another 5 ml of the lidocaine solution injected subcutaneously.

Patients were examined in the perioperative period for clinical evidence of pneumothorax. During a postoperative interview, questions concerning comfort during performance of the block and subsequent quality of surgical anesthesia were asked to assess overall patient satisfaction.

Results

The first rib was readily palpated in all patients. In the three patients in whom first rib needle contact was sought, the needle was placed directly on the rib

Figure 4. Index and long fingers defining the margins of the first rib.

Figure 5. Needle placement for supraclavicular brachial plexus block. The needle is placed between the fingertips, perpendicular to the skin in all planes.

on the first attempt. There were no anesthetic failures. The ulnar nerve was incompletely anesthetized 10 minutes following the block in two patients and was successfully blocked at the elbow. No patient complained of shortness of breath or showed any evidence of pneumothorax. However, we cannot exclude the possibility of subclinical pneumothorax, as chest radiographs were not performed in all patients. Horner's syndrome was apparent on the ipsilateral side in all patients. There were no other complications and patient satisfaction was excellent.

Discussion

Previous descriptions (3) of supraclavicular brachial plexus block all describe placing the needle at an arbitrary point on the skin and then contacting the first rib with the needle. This involves a certain amount of guesswork. If the anesthetist guesses wrong, either through inexperience or because of anatomic variability, the needle may inadvertently contact the dome of the lung resulting in a pneumothorax. This relatively common problem has been noted to occur in up to 5% of cases (1). We describe a new technique that positively locates the first rib by palpation prior to needle insertion and takes the

guesswork out of the procedure. Our experience with 28 patients and many test subjects confirms that this landmark may be readily palpated in all but the most morbidly obese. The first rib, serving as a safety "backstop" to prevent lung injury, also defines the posterior border of the compartment containing the brachial plexus at the level of the clavicle. Also, if one introduces the needle at the lateral border of the first rib, and the tip is deeper than the subcutaneous tissue, it should be in the proper compartment. This makes the block particularly easy to teach and master.

The advantages of supraclavicular block are many. The brachial plexus is most compact at the level of the three trunks and has minimal fascial subcompartmentalization. This factor allows rapid onset and more complete spread of anesthesia so that the entire plexus, including axillary and musculocutaneous nerves, are readily blocked. The technique can be performed with the arm in virtually any position without affecting the spread of local anesthetic (1), which is particularly advantageous when ability to abduct the arm is limited, such as by pain secondary to traumatic injury or mechanical interference from orthopedic fixation devices.

Disadvantages of the block, as classically described (3), include difficulty of mastering the technique and an often unacceptably high incidence of pneumothorax (1). These problems account for the limited popularity of the procedure. Other complications include phrenic nerve block (40–60%) and Horner's syndrome (70–90%) (1). The high incidence of phrenic nerve block dictates that the primary contraindication to supraclavicular block is respiratory insufficiency. Bilateral supraclavicular blocks should not be performed on any patient to avoid the risk of bilateral phrenic nerve paralysis.

Palpation of the first rib is similar in sensation to palpation of Chassaignac's tubercle (transverse process of C6), a landmark for stellate ganglion block (4). The rib lies under several centimeters of soft tissue in the supraclavicular fossa, yet may be reliably defined with practice. The medial border of the first rib is most superficial and often easier to palpate than the deeper, lateral border. The technique of first rib location may be best learned by beginning palpation on slender subjects. Those who have attempted to learn this technique have, in short time, been able to locate the first rib rapidly and with confidence. After the margins of the rib are defined between index and long fingers, the plexus is readily located between the fingertips, 2–3 cm deep in the skin, usually on the lateral aspect of the rib, lateral to the subclavian artery that is often palpable (Fig. 2). Although this study does not exclude the possibility of lung injury, with definite identification of the first rib, one should be able to seek paresthesias with a reduced risk of pneumothorax.

In summary, we describe palpation of the first rib as the primary landmark in performing supraclavicular brachial plexus blockade. Our experience, reported here, demonstrates that this technique has advantages over those previously described in that it is simple, reliable, and may reduce the potential of pneumothorax.

References

1. Bridenbaugh LD. The Upper Extremity: Somatic Blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural Blockade. Philadelphia: JB Lippincott, 1988:393–7.

2. Carron H, Korbon GA, Rowlingson JC. Regional Anesthesia: Techniques and Clinical Applications. Orlando: Grune & Stratton, 1984:25.

3. Winnie AP. Plexus Anesthesia. Philadelphia: WB Saunders, 1983;85:92.

4. Supra note 2, p. 134.

Pulmonary Edema and Coagulopathy Due to Hyskon® (32% Dextran-70) Administration

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Gynecologists use Hyskon® (32% dextran-70, Hyskon Division, Pharmacia, Piscataway, New Jersey) to improve visualization during diagnostic and therapeutic hysteroscopy. Zbella et al. (1) reported a case of pulmonary edema and coagulopathy, and Leake et al. (2) reported two cases of noncardiogenic pulmonary edema without coagulopathy associated with the use of Hyskon®. Because these reports appeared in a journal not generally read by anesthesiologists, and since anesthesiologists are likely to be the first physicians to observe this complication in practice, we report the following case.

Case Report

A 46-year-old, 47-kg, 153-cm woman with treated hypothyroidism, asymptomatic mitral valve prolapse, and allergy to iodine presented for hysteroscopic laser myomectomy. Preoperative physical examination revealed no heart murmur and the lungs were clear. The serum electrolytes and blood urea nitrogen (BUN) levels, urinalysis, chest radiograph, and electrocardiogram were within normal limits. The hematocrit was 41.2%.

After premedication with 5 mg of diazepam, anesthesia was induced with 100 μg of fentanyl and 200 mg of thiopental. Atraumatic orotracheal intubation was performed with a 6.5-mm cuffed tube facilitated by 80 mg of succinylcholine. Anesthesia employing controlled mechanical ventilation (rate 8 per minute, TV 600 ml) throughout surgery was maintained with

67% N_2O, 33% O_2, and 0.2 to 0.6% inspired isoflurane; muscle relaxation was provided by a total of 35 mg of atracurium.

Surgery employing simultaneous hysteroscopy and laparoscopy was uneventful for the first 90 minutes. At that time, peak airway pressure increased from 32 to 40 cm H_2O, followed within 5 minutes by a decrease in arterial saturation determined by pulse oximetry from 99% at an F_1O_2 of 0.30 to 96% at an F_1O_2 of 0.50, and simultaneous appearance of 50 ml of bloody sputum in the tracheal tube. There was no change in heart rate and blood pressure, but auscultation of the lung fields revealed bilateral coarse rales. Furosemide (20 mg) was given and repeated in 5 minutes, with no effect on urine output through a newly inserted Foley catheter. The surgical procedure was terminated. The patient awakened in the operating room and the tracheal tube was removed. Fluids given included 650 ml of intravenous crystalloid and 900 ml of intrauterine Hyskon®. Blood loss was 250 ml and urine output was 50 ml.

In the recovery room, an additional 100 mg of furosemide was given, but still without diuresis. Physical examination revealed bilateral coarse rales throughout both lungs, no jugular venous distension in the 30° head-up position, and no heart murmur or gallop. Chest x-ray study showed a normal heart size and bilateral alveolar pulmonary edema. Copious but unmeasured blood loss per vagina was noted. The hematocrit decreased to 23%, presumably because of the vaginal bleeding. Prothrombin time was 13.5/12.1 seconds, partial thromboplastin time (PTT) 53.1/29.9 seconds, thrombin time 13.3 seconds, fibrinogen level 107 mg/dl, fibrin split products <10 μg/ml, and platelet count 69,000/mm^3. An arterial blood sample had a pH of 7.36, PCO$_2$ of 36 mm Hg, and PO$_2$ of 68 mm Hg while the patient breathed >60% O_2 by face mask. The PO$_2$ gradually increased to 117 mm Hg, with an F_1O_2 of 0.5 before discharge to the intensive

care unit 4 hours later. Two units of fresh frozen plasma were administered, on the advice of a hematology consultant, to correct the PTT. Hemoptysis, coagulopathy, and vaginal bleeding eventually ceased.

While in the intensive care unit, the patient continued to cough up bloody sputum for several hours. Oxygenation and urinary output gradually improved, and she was discharged from the hospital 6 days later with a normal coagulation profile and a hematocrit of 24%. We believe that the decrease in hematocrit was due to the vaginal bleeding on the day of surgery rather than hemolysis, since the postoperative LDH level was 100 units/liter (normal 94 to 200).

Discussion

Lukascko (3) stated that volumes of Hyskon® >500 ml given intravenously may cause pulmonary edema by plasma volume expansion. Because of its osmotic properties, every 100 ml is expected to expand the plasma volume by 860 ml (3). Cleary et al. (4) observed clinical ascites 2 days after intraperitoneal instillation of 250 ml of Hyskon®, but no dextran was found in serum for the first 24 hours.

We believe that noncardiogenic pulmonary edema developed in this patient based on her negative cardiac history, the volumes and types of fluids given intraoperatively, the findings of postoperative physical examination, the lack of response to furosemide, normal serum levels of cardiac enzymes postoperatively, a normal postoperative electrocardiogram, and concurrent large blood loss per vagina. Noncardiogenic pulmonary edema is probably a result of a direct toxic effect on the pulmonary capillaries following intravascular absorption of Hyskon®. The mechanism is similar to the drug-induced noncardiogenic pulmonary edema reported with methadone, heroin, propoxyphene, salicylates, and dextran-40 (1,6). Fluid overload cannot be ruled out because invasive monitoring was not performed as a result of the patient's coagulopathy and steadily improving pulmonary condition. It is possible but unproven that the significant vaginal blood loss served as inadvertent treatment for Hyskon®-induced fluid overload.

Dextrans have been associated with various clinical and laboratory abnormalities. Dextran-40 can cause factitious elevations in blood glucose, errors in blood cross-matching, decreased platelet adhesiveness, renal failure, and decreased plasma levels of fibrinogen and factors V, VIII, and IX (5). Dextran-40 has also been shown to cause noncardiogenic pulmonary edema (6). An anaphylactoid reaction as a cause of noncardiogenic pulmonary edema seems unlikely in our patient in the absence of laryngeal edema, urticaria, and hypotension.

Forty-two cases of laser hysteroscopy had been studied at our institution before this case. Hyskon® was used in only 22 of them, but in all of the last 16. The mean dose ± standard deviation was 480 ± 236 ml. None of the other patients developed alveolar pulmonary edema, but one patient given 600 ml Hyskon® developed postoperative hypoxia requiring supplemental oxygen, and three other patients were given furosemide prophylactically to induce diuresis to avoid fluid overload.

In summary, we report a case of coagulopathy and pulmonary edema, without evidence of allergic reaction, presumed to be secondary to Hyskon® administration. Although the effect may have been due to fluid overload, we feel the evidence favors direct pulmonary toxicity. In any event, anesthesiologists should be aware of the volume of Hyskon® used intraoperatively, its potential complications, and the fact that some investigators (1,2) recommend that not >500 ml be given.

References

1. Zbella EA, Moise J, Caisan SA. Noncardiogenic pulmonary edema secondary to intrauterine instillation of 32% dextran 70. Fertil Steril 1985;43:479-80.

2. Leake JF, Murphy AA, Zacur HA. Noncardiogenic pulmonary edema: a complication of operative hysteroscopy. Fertil Steril 1987;48:497-9.

3. Lukascko P. Noncardiogenic pulmonary edema secondary to intrauterine instillation of 32% dextran 70. Fertil Steril 1985;44:560-1.

4. Cleary RE, Howard T, DeZerega GS. Plasma dextran level after abdominal instillation of 32% dextran 70: evidence for prolonged intraperitoneal retention. Am J Obstet Gynecol 1985;152:78-9.

5. Data JL, Nies AS. Drugs five years later: dextran 40. Ann Intern Med 1974;81:500-4.

6. Kaplan AI, Sabin S. Dextran 40: another cause of drug-induced noncardiogenic pulmonary edema. Chest 1975;68:376-7.

Possible Malignant Hyperthermia in a 7-Week-Old Infant

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Key Words: HYPERTHERMIA, MALIGNANT.

Malignant hyperthermia (MH) is a serious and potentially life-threatening complication associated with certain inhalation anesthetics and neuromuscular relaxants. It is an uncommon condition, occurring in approximately 1 among 50,000 anesthetics administered to adults and 1 among 15,000 of those administered to children (1). The youngest patient previously reported to have MH was 3 months of age (2). Here, we report on the development of events that possibly represented MH in a 7-week-old infant given halothane and succinylcholine during induction of anesthesia for repair of an inguinal hernia.

Case Report

A 7-week-old white male infant weighing 3.9 kg was referred to our hospital for critical care management after complications associated with anesthetic induction at another hospital.

The patient was admitted to the referring hospital on the day prior to surgery. The infant had no prior medical problems. He was delivered at 37 weeks' gestational age by uncomplicated cesarean section performed for late decelerations from a nuchal cord. The patient weighed 2.4 kg at birth and had no problems after delivery. Preoperative hemoglobin was 11.1 mg%.

At the referring hospital, the infant was taken to the operating room, where a precordial stethoscope and monitors of the electrocardiogram, blood pressure, temperature, and a pulse oximeter were applied. Anesthesia was induced with nitrous oxide, oxygen, and halothane administered via mask. A peripheral intravenous catheter was inserted; 0.04 mg of glycopyrolate and then 4 mg/kg of succinylcholine

as a bolus were administered to facilitate intubation. The patient immediately became gray, developed rigidity of his extremities, and was difficult to ventilate because of apparent masseter muscle spasm. The pulse oximeter indicated rapid arterial oxygen desaturation and the heart rate decreased from 100 to 70 beats/min. An endotracheal tube was quickly placed without difficulty; halothane was discontinued and 100% oxygen was given, with an immediate increase in the oxygen saturation to 100%. Simultaneously, the heart rate increased to 130 beats/min and systolic blood pressure obtained at that time was 70 mm Hg. The muscle rigidity resolved over the next few minutes. Premature ventricular contractions with two brief self-limited episodes of ventricular tachycardia developed over the next 20 min. The patient's blood pressure was adequate throughout this period, and no chest massage or pharmacologic cardiovascular support was necessary. Dantrolene sodium 4 mg (1 mg/kg) was administered approximately 30 min after succinylcholine had been given. An arterial sample obtained 50 min after administration of the succinylcholine revealed a pH of 7.13, a partial pressure of carbon dioxide ($Paco_2$) of 62 mm Hg, and a partial pressure of oxygen (Pao_2) of 248 mm Hg. Serum electrolyte levels also obtained at that time included a sodium of 127 mEq/L, a potassium of 6.5 mEq/L, a chloride of 102 mEq/L, and a CO_2 of 26 mEq/L (venous plasma CO_2 combining power). After the blood gas data were obtained, 4 mEq of sodium bicarbonate was administered. Serum creatine kinase (CK) level at this time was later reported to be zero. Skin temperature was 96°F (35.5°C) initially and did not change during the acute event. The heart rate had increased in the hour after the succinylcholine administration to 180 to 190 beats/min, and the blood pressure had also increased to 110 to 120 mm Hg systolic pressure.

The patient was then moved to the recovery room. Vital signs were normal, and he had good muscle tone and respiratory function. The endotracheal tube was removed. An arterial blood sample obtained at this time, approximately 2 hours after the succinyl-

choline was administered, showed a pH of 7.31, $Paco_2$ of 42 mm Hg, and Pao_2 of 64 mm Hg while the patient was being given O_2 by mask (FiO_2 0.4). Because the infant's respiratory rate was 80 to 90 per minute, however, the patient was reintubated. In light of the residual metabolic acidosis and the small dose of dantrolene initially administered, an additional 1 mg/kg of dantrolene was given. The patient's skin temperature was still 96°F (35.5°C). He was then transferred, accompanied by the referring anesthesiologist, to our hospital.

On arrival, approximately 4 hours after the succinylcholine was given, the patient had normal vital signs, a rectal temperature of 96.1°F (35.6°C), and clear lungs. The initial arterial blood sample at our institution (FiO_2 1.0) had a pH of 7.32, $Paco_2$ of 40 mm Hg, and Pao_2 of 402 mm Hg. The tracheal tube was removed and the patient maintained excellent oxygenation and ventilation. Serum electrolyte levels obtained shortly after arrival included a sodium of 133 mEq/L, a potassium of 4.5 mEq/L, a chloride of 104 mEq/L, and a CO_2 of 18 mEq/L. Initial serum CK level also obtained at that time was 111,200 units/liter, with a zero MB fraction. Urinalysis revealed large amounts of myoglobinuria.

The infant was admitted to our pediatric intensive care unit. Because of the favorable response to 1 mg/kg of dantrolene given previously, this dose was repeated at 6-hour intervals for 24 hours. The patient was also given a sodium bicarbonate infusion (0.25 mEq/kg per hour) to maintain an alkaline urine to facilitate myoglobin excretion. Monitoring consisted of rectal temperature, electrocardiogram, respirations, and pulse oximetry, along with frequent measurement of vital signs.

The patient's next 36 hours were uneventful. Serum electrolyte levels and blood gas tensions remained normal, and the urine gradually cleared of myoglobin. Thirty-six hours after admission, the patient's left lower lung lobe became atelectatic as a result of a mucous plug; intubation and ventilatory support were required for 48 hours. The patient received another 24 hours of dantrolene therapy after being intubated as prophylaxis against recrudescence of possible MH.

Serum CK levels never returned to normal during the 5-day hospitalization, but stabilized at 5765 to 6365 units/liter before discharge. Of interest were the serum CK-MB fractions, which increased after the initial value of zero to a peak of 4.9% (1260 units/liter MB, with a total of 25,720 units/liter) 48 hours after admission. Echocardiography performed on the second hospital day revealed no wall motion abnormal-

ities and normal contractility. There were no arrhythmias after the initial arrhythmias seen during the initial acute event.

The patient was discharged home on day 6 after the initial event, completely recovered except for residual elevation of serum CK values. He was scheduled to return to our institution for repair of his inguinal hernia. A blood sample obtained 15 days after the initial episode had a CK level of 2080 units/liter. The patient's family has no history of anesthetic complications. There is no family history of sudden infant death syndrome (SIDS) or musculoskeletal disease, and this infant is an only child. Both parents declined muscle biopsy testing for MH susceptibility.

The patient returned to our hospital 3 months after the episode of possible MH for repair of his inguinal hernia. The patient had no problems during that time and weighed 6.2 kg. The admission CK value was 15,000 units/liter, and serum electrolytes were normal.

The patient was brought to the operating room with no premedication; dantrolene sodium therapy was not instituted. An intravenous cannula was placed after the patient had methohexital (30 mg/kg) instilled rectally. The patient then received vecuronium bromide (0.1 mg/kg), sodium thiopental (4 mg/kg), and fentanyl citrate (3.5 µg/kg). After muscle relaxation was obtained, the patient had an endotracheal tube placed. The anesthetic was maintained with nitrous oxide, oxygen, and fentanyl in a total dose of 5 µg/kg. An arterial blood sample obtained during the procedure revealed no metabolic acidosis and a normal potassium of 4.1 mEq/L. A muscle biopsy was obtained from the right quadriceps muscle during the procedure. At the end of the operation, the neuromuscular blockade was reversed with neostigmine (0.07 mg/kg), with 0.02 mg/kg of atropine sulfate also administered. The patient was extubated after adequate reversal of the neuromuscular blockade and after the patient became responsive. The patient's postoperative course was uneventful, with no evidence of MH by clinical or laboratory examinations.

The muscle biopsy specimen was examined by both light and electron microscopy. The specimen had histopathology consistent with Duchenne's muscular dystrophy. Our laboratories do not have the capacity to perform caffeine contracture testing, and our patient's family had no resources to travel to a center where this is available. The patient is now living at home with his parents and has no apparent problems.

Discussion

This case is unique in that an episode of possible MH occurred in a 7-week-old infant, the youngest case yet reported. Sewall et al. (3) made a diagnosis of probable MH in a newborn with muscular rigidity delivered by cesarean section, but that infant had no direct anesthetic exposure. The youngest case of MH reported in the literature before this was in a 3-month-old Lumbee Indian infant (2). The youngest patient previously reported to have Duchenne's muscular dystrophy associated with either an anesthetic-induced rhabdomyolysis or MH was 21 months of age (4). Our patient had many of the signs of MH after administration of halothane and a large dose (4 mg/kg) of succinylcholine, two known triggering agents (5). Gronert et al. (6) state that excessive striated muscle depolarization may be a factor in the etiology of MH. Although our patient's episode could have occurred with any dose of succinylcholine, the reaction may have been exacerbated by the large dose. Signs of MH included diffuse muscular rigidity, tachycardia, tachyarrhythmias, rapid arterial oxygen desaturation, myoglobinuria, and metabolic acidosis (7). The infant did not have a temperature increase, but this may have been because of the rapid institution of dantrolene sodium therapy and the previously reported factor of rapid heat loss in an exposed infant (8). Also, an increase in temperature is a relatively late finding in MH compared with muscular rigidity, hypercarbia, and arrhythmias (5).

During the second anesthetic, the patient had a muscle biopsy performed. The muscle biopsy was diagnostic for Duchenne's muscular dystrophy. This is not a surprising finding in light of the continued elevations of CK. There are many reports in the literature of rhabdomyolysis, cardiac dysrhythmias, and even death in patients with Duchenne's muscular dystrophy after the administration of succinylcholine (9–12). Most of these episodes of rhabdomyolysis occurred in patients with some clinical signs of Duchenne's muscular dystrophy, whereas our patient was and continues to be asymptomatic for muscular dystrophy. It is also accepted that there is an association between Duchenne's muscular dystrophy and MH (8,13–15). In our patient, the presence of tachyarrhythmias, elevated CK, hyperkalemia, and myoglobinuria is consistent with the occurrence of either succinylcholine-induced rhabdomyolysis or MH. Our patient had an increase in CK to a peak >100,000 units/liter. This increase, in light of the return to an apparent baseline CK of approximately 2000 units/liter, is much greater than the 10-fold

increase in CK that Ryan (16) has suggested to be indicative of MH. The severe metabolic and respiratory acidosis that our patient exhibited are typical of MH, but have also been reported previously in a patient with Duchenne's muscular dystrophy during a rhabdomyolysis reaction to succinylcholine (9). In our patient, cardiovascular instability with hypoperfusion is not an adequate explanation for the metabolic acidosis because bradycardia was present only briefly during the placement of the endotracheal tube, the two episodes of ventricular tachycardia were brief and self-limited, and the blood pressure was either normal or elevated throughout the episode. The absence of an increase in temperature also is not inconsistent with MH since a lack of increase in temperature has been previously reported in several children with Duchenne's muscular dystrophy who developed MH (8,13,14). In general, anesthesia for patients with Duchenne's muscular dystrophy is not associated with significant problems. Cobham and Davis (17) and Richards (18) reported a combined total of 161 anesthetics in these patients without incident. Given the reports by Brownell et al. (13), Kelfer et al. (14), and Wang and Stanley (8) of the association between MH and Duchenne's muscular dystrophy, we feel that this patient may have experienced an episode of MH; however, we cannot completely exclude the possibility that the patient had succinylcholine-induced rhabdomyolysis.

Postoperatively, the patient did well considering the rapidity and severity of the presentation of the possible MH. An interesting finding was the presence of a 5% MB fraction of the CK. The elevated CK-MB was not found in the initial CK level, but was present in later samples. Mayhew et al. (19) reported finding both the MB and BB isoenzymes of CK in the serum of a 6-month-old infant after an episode of MH. The infant in Mayhew's report did not have muscular dystrophy. Cardiac involvement is common in Duchenne's muscular dystrophy, but usually only when the disease has progressed clinically (9). This may explain the elevation of the CK-MB isoenzyme in our patient. However, the infant in our case had no cardiovascular instability after the acute episode, and had a normal echocardiogram on the second hospital day. The normal echocardiogram and enzyme changes indicated that the patient apparently had a diffuse myocardial injury unassociated with any persistent cardiovascular instability, and which 2 days after the possible MH reaction had no discernable effect on myocardial contractility. Gronert et al. (6) stated that the heart is involved in MH, but whether a primary myocardial abnormality is present

or whether the heart is secondarily damaged by the high circulating levels of catecholamines is unknown. The CK-MB levels declined in our patient after peaking on day 2 after the acute episode, and the CK-BB isoenzyme was not detected at any time.

In our case, the infant had no conditions detected preoperatively that are associated with an increased risk of MH. The 3-month-old Lumbee Indian infant had known congenital mesenchymal tissue abnormalities and muscular skeletal disorders, which have been associated with an increased incidence of MH (2). Postoperatively, our patient continued to have an elevated CK level, and after muscle biopsy was diagnosed as having Duchenne's muscular dystrophy. This elevated CK level was not detected preoperatively because CK levels are not a routine preoperative screening test in pediatric patients in either our own or the referring institution. Preoperative CK levels have been shown to be of no value as a screening test for MH susceptibility (20). This infant's family has no history of muscular dystrophies or myopathies or SIDS, the latter of which is consistent with recent reports that there is no association between MH and SIDS (21).

In conclusion, we report the unexpected occurrence of a possible episode of MH in a previously healthy 7-week-old infant who had no known risk factors for the development of MH. He is the youngest patient reported in the medical literature to have had a probable episode of MH or anesthetic-induced rhabdomyolysis. This case emphasizes the need to be constantly vigilant for the occurrence of MH in all patients, regardless of age. The acute episode developed after administration of halothane and succinylcholine, two well-documented triggering agents for MH. He then had a rapid recovery from this event after dantrolene sodium therapy. The very large increase in his CK level included an increase in the serum CK-MB isoenzyme. This increase in the MB isoenzyme was not associated with any clinical or echocardiographic cardiovascular abnormalities after the acute event. The patient then had an uneventful anesthetic administered without triggering agents 3 months after the first occurrence. During this procedure, a muscle biopsy was performed and was diagnostic for Duchenne's muscular dystrophy. The patient's family has no history of anesthetic complications, musculoskeletal diseases, or SIDS. Although rhabdomyolysis must be considered as a possible cause of the acute episode in this patient, we feel that MH is the most probable explanation in light of the severe metabolic and respiratory acidosis that were present.

References

1. Britt BA. Recent advances in malignant hyperthermia. Anesth Analg 1972;51:841-50.

2. Bailey AG, Bloch EC. Malignant hyperthermia in a three-month-old American Indian infant. Anesth Analg 1987;66: 1043-5.

3. Sewell K, Flowerdew RMM, Bromberger P. Severe muscular rigidity at birth: malignant hyperthermia syndrome? Can Anaesth Soc J 1980;27:279-82.

4. Oka S, Igarashi Y, Takagi A, et al. Malignant hyperpyrexia and Duchenne muscular dystrophy: a case report. Can Anaesth Soc J 1982;29:627-9.

5. Britt BA. Malignant hyperthermia. Can Anaesth Soc J 1985;32: 666-77.

6. Gronert GA, Mott J, Lee J. Aetiology of malignant hyperthermia. Br J Anaesth 1988;60:253-67.

7. Rosenberg H. Clinical presentation of malignant hyperthermia. Br J Anaesth 1988;60:268-73.

8. Wang JM, Stanley TH. Duchenne muscular dystrophy and malignant hyperthermia—two case reports. Can Anaesth Soc J 1986;33:492-7.

9. Miller ED, Sanders DB, Rowlingson JC, Berry FA, Sussman MD, Epstein RM. Anesthesia-induced rhabdomyolysis in a patient with Duchenne's muscular dystrophy. Anesthesiology 1978;48:146-8.

10. McKishnie JD, Muir JM, Girvan DP. Anaesthesia induced rhabdomyolysis—a case report. Can Anaesth Soc J 1983;30: 295-8.

11. Seay AR, Ziter FA, Thompson JA. Cardiac arrest during induction of anesthesia in Duchenne muscular dystrophy. J Pediatr 1978;93:88-90.

12. Henderson WAV. Succinylcholine-induced cardiac arrest in unsuspected Duchenne muscular dystrophy. Can Anaesth Soc J 1984;31:444-6.

13. Brownell AKW, Paasuke RT, Elash A, et al. Malignant hyperthermia in Duchenne muscular dystrophy. Anesthesiology 1983;58:180-2.

14. Kelfer HM, Singer WD, Reynolds RN. Malignant hyperthermia in a child with Duchenne muscular dystrophy. Pediatrics 1983;71:118-9.

15. Brownell AKW. Malignant hyperthermia: relationship to other diseases. Br J Anaesth 1988;60:303-8.

16. Ryan J. Malignant Hyperthermia. In: Ryan JH, Todes ID, Cote CJ, Goudsouzian N, eds. A Practice of Anesthesia for Infants and Children. Orlando, Florida: Grune and Stratton, 1986:243-51.

17. Cobham IG, Davis HS. Anesthesia for muscle dystrophy patients. Anesth Analg 1964;43:22-9.

18. Richards WC. Anaesthesia and serum creatine phosphokinase levels in patients with Duchenne's pseudohypertrophic muscular dystrophy. Anaesth Intens Care 1972;1:150-3.

19. Mayhew JF, Rudolph J, Tobey RE. Malignant hyperthermia in a six-month-old infant: a case report. Anesth Analg 1978;57: 262-4.

20. Paasuke RT, Brownell AKW. Serum creatine kinase level as a screening test for susceptibility to malignant hyperthermia. JAMA 1986;255:769-71.

21. Ellis FR, Halsall PJ, Harriman DGF. Malignant hyperpyrexia and sudden infant death syndrome. Br J Anaesth 1988;60:28-30.

Probable Seizure after Alfentanil

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There have been several case reports of seizure-like activity associated with fentanyl (1–3) and sufentanil (4–6) during induction of anesthesia as well as postoperatively (7). As yet there have been no reports of such activity described with alfentanil.

Case Report

A 60-year-old, 70-kg male was scheduled for an L4–5 laminectomy/discectomy. He had a history of atherosclerotic heart disease with prior myocardial infarction in 1981 and stable angina. He also had a history of atherosclerotic peripheral vascular disease with prior abdominal aortic aneurysm repair in 1982. His medications included propranolol, dipyridamole, isosorbide, and diazepam. He had no prior history of a seizure disorder or other neurologic disease. Except for a slightly decreased left patellar tendon reflex and back tenderness, his physical examination was within normal limits.

The patient was given his usual cardiac medications plus, one hour prior to surgery, metoclopramide 10 mg, ranitidine 150 mg and diazepam 5 mg. He also received 1 mg of midazolam iv just prior to entering the operating room. He was monitored with an EKG, an automated sphygmomanometer, a precordial stethoscope, and a pulse oximeter prior to, during, and after induction of the anesthesia. Following the preoxygenation, he was given 1500 μg of alfentanil (25 μg/kg) over 30 seconds. He developed a tremor in the right arm, and then in the left arm, followed by coarse jerking movements of both legs. The movement became progressively more rhythmic and coarse. Then his eyes rolled up and he became

unresponsive. The oxygen saturation was 96–97% and he continued to breathe up until he lost consciousness. The shaking movements continued for about 30 seconds, at which time he was given 100 mg of thiopental and the activity stopped immediately. The patient's lungs were ventilated easily and the induction was completed with a total of 50 μg/kg of alfentanil, 10 mg vecuronium, and 150 mg thiopental. Following the tracheal intubation, anesthesia and surgery proceeded without further difficulty. The patient was awake and responsive at the end of the surgery at which time the tracheal tube was removed. On the first postoperative day the patient was noted to have a new left facial droop, slurred speech, and right-sided weakness. Clinically diagnosed as a left cerebral vascular accident, the CT scan of the head was unremarkable. Three days postoperatively the neurologic deficits were largely resolved. An EEG was not obtained.

Discussion

The most common cause of seizures in the elderly population is cerebrovascular disease (8). Other common causes, such as a brain tumor, metabolic disorder, hepatic failure, cerebral infection, electrolyte abnormality, and hypoglycemia, were not present in our patient. Since most seizures resolve without neurologic sequela, one possible explanation for this patient's unfortunate outcome was that he had an undetected preexisting cerebral infarct which became manifest during the induction of anesthesia, i.e., a partial seizure progressed to a generalized seizure, and was manifest further postoperatively with focal deficits. Another possibility is that this patient's seizure was complicated by a temporary postictal paralysis (Todd's paralysis). Collier and Engelking (9) recently described such a case following an interscalene block with paralysis resolving within 24 hours. Although uncommon, this condition is well recognized in the neurology literature and may be due either to focal epileptic discharge leading to local vasomotor and/or metabolic changes (10), or to active

inhibition of neuronal function (11). In either case, given the temporal relationship, alfentanil was the most likely stimulus for the ensuing seizure-like activity.

Other drug interactions cannot be excluded as a cause for the neurologic response seen in this patient. For example, metoclopramide is associated with extrapyramidal symptoms (1 in 500) (12), as well as a few isolated reports of convulsive seizures, without a clear-cut relationship to metoclopramide. The other drugs given prior to alfentanil either raise the seizure threshold (diazepam and midazolam), or have not been reported as convulsants, neither alone nor in combination with other drugs. Again, the time course favors alfentanil as the most probable stimulus for the seizure activity observed in the patient.

All narcotics have been shown to induce seizures in laboratory animals (13,14) when given in high doses. The apparent seizures associated with fentanyl and sufentanil in previous case reports were not documented by EEG. Some (15,16) suggest that un-modified muscle rigidity commonly seen with narcotics is mistaken for seizure activity. Indeed, Sebel et al. (17) and Bovill, et al. (18) continuously monitored EEGs during high dose fentanyl and sufentanil anesthesia and noted no EEG seizure activity, although they did note some sharp wave activity of unclear etiology. Benthuysen, et al. (19) monitored EEGs and EMGs during alfentanil administration and found marked rigidity in all muscle groups but no seizure activity. This rigidity appears to be centrally mediated and can be attenuated with naloxone, with the mechanical difficulties associated with seizures overcome with small doses of muscle relaxants.

Our case report along with several others contain aspects that contradict the theory that seizure-like movements are simply exaggerated muscle rigidity. First, many of the reports, including ours, involved relatively small doses of narcotics. Rigidity is usually dose related and only marked at higher doses. Second, our patient responded immediately to a small dose of thiopental as did several of the cases reported by others. Again, this is more consistent with seizure activity, not primary muscle rigidity. Finally, our patient developed a neurologic sequela, or a transient stroke. Whether this was a cause/effect relationship is unknown, but it is inconsistent with muscle rigidity, and is very disconcerting.

In summary, although not documented by EEG, we describe a patient who clinically had seizure activity following a small dose of alfentanil not associated with hypoxia or hypercarbia. The patient suffered an apparent cerebral vascular accident perioperatively. Further investigation into possible narcotic induced seizure activity is warranted.

References

1. Rao TLK, Mummaneni N, El-Etr AA. Convulsions: an unusual response to intravenous fentanyl administration. Anesth Analg 1982;61:1020-1.
2. Safwat AM, Daniel D. Grand mal seizure after fentanyl administration. Anesthesiology 1983;59:78.
3. Holen AO. Another case of grand mal seizure after fentanyl administration. Anesthesiology 1984;60:387-8.
4. Molgegott LP, Flashburg MH, Karasic L, Karlin BL. Probable seizures after sufentanil. Anesth Analg 1987;66:91-3.
5. Brian JE, Seifen AB. Tonic-Clonic activity after sufentanil. Anesth Analg 1987;66:481.
6. Rosman EJ, Capan LM. Another case of probable seizure after sufentanil. Anesth Analg 1987;66:913.
7. Goroszeniuk T, Albin M, Jones RM. Generalized grand mal seizure after recovery from uncomplicated fentanyl-etomidate anesthesia. Anesth Analg 1986;65:979-81.
8. Dichter MA. The epilepsies and convulsive disorders. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. New York: McGraw-Hill Book Company, 1983:2018-28.
9. Collier HW, Engelking K. Todd's paralysis following an interscalene block. Anesthesiology 1984;61:342-3.
10. Yarnell PR. Todd's paralysis: a cerebrovascular phenomenon. Stroke 1975;6:301-3.
11. Efron R. Post-epileptic paralysis: theoretical critique and report of a case. Brain 1961;84:381-94.
12. Physicians Desk Reference. Product information section for metoclopramide. 42nd edition. Oradell, NJ, Medical Economics Company, 1988:1696-8.
13. Carlsson C, Smith DS, Keykhah MM, Englebach I, Harp JR. The effects of high-dose fentanyl on cerebral circulation and metabolism in rats. Anesthesiology 1982;57:375-80.
14. deCastro J, van de Water A, Wouters L, Xhanneux R, Reneman R, Kay B. Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Acta Anaesthesiol Belg 1979;30:6-99.
15. Sebel PS, Bovill JG. Fentanyl and convulsions. Anesth Analg 1983;62:858.
16. Benthuysen JL, Stanley TH. Concerning the possible nature of reported fentanyl seizures. Anesthesiology 1985;62:205.
17. Sebel PS, Bovill JG, Wauquier A, Rog P. Effects of high-dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 1981;55:203-11.
18. Bovill JG, Sebel PS, Wauquier A, Rog P. Electroencephalographic effects of sufentanil anaesthesia in man. Br J Anaesth 1982;54:45-52.
19. Benthuysen JL, Ty Smith N, Sanford TJ, Head N, Dec-Silver H. Physiology of alfentanil-induced rigidity. Anesthesiology 1986;64:440-6.

Long-Term Post-Thoracotomy Cancer Pain Management with Interpleural Bupivacaine

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The physician managing pain in cancer patients needs to be able to draw on a large variety of drugs and techniques. Reiestad and Strömskag (1) have recently introduced the interpleural injection of local anesthetics as a technique for managing postoperative pain in patients undergoing various procedures. Subsequently, several studies have appeared in the literature which have expanded on that technique. All except one (2) have dealt exclusively with patients experiencing acute pain of nonmalignant cause in postoperative or posttraumatic situations. More importantly, pleural fibrosis has been suggested as a relative contraindication to interpleural analgesia, presumably because pleural thickening and fibrosis may inhibit the spread of the anesthetic solution and result in suboptimal analgesia. Recently, I treated a patient with chronic pain due to chest wall metastases, who not only had a previous thoracotomy and lobectomy, but also widespread postoperative pulmonary and pleural fibrosis.

Previous reports have described only acute short term use of an interpleural catheter. The present case report demonstrates that interpleural installation of local anesthetics can be effective for at least 2 months, and also, as will be described, is an efficacious route of administration of other analgesics.

Case Report

A 58-year-old woman with bronchogenic carcinoma metastatic to the right pleural area and contiguous with the chest wall was referred to the Anesthesiology Department for assistance with pain control. She had been a heavy smoker with a cough. Carcinoma of the right lung was diagnosed 2 years previously, and soon thereafter she had a thoracotomy with a right upper lobectomy. Treatment since then consisted of oral analgesics, progressing to control-release oral morphine sulfate (15 mg) every 3 hours and radiotherapy to the chest. Although there were numerous metastases, those of greatest concern were in the right pleura and chest wall, causing unrelenting pain. This pain was continuous and exacerbated by any movement involving chest wall muscles. Sitting upright was difficult. She could locate the painful region to the anterior axillary line at about T4 to T6 of the right chest wall, but the site of pain was not discreet enough to pinpoint with a finger. If the pain from that site were to be relieved, she could possibly sit upright at ease and sleep at night. Pain in other areas paled in importance compared with that which she suffered in her right chest wall.

Physical examination revealed a small cachectic woman guarding against movement. She was fearful and dubious of assistance. Her height was 157 cm and weight was 38 kg. Rhonchi were audible throughout both lungs, and breath sounds were diminished slightly on the right. Chest x-ray study showed the right chest to be status post-thoracotomy with extensive fibrous changes, pleural thickening, fluid, and lytic lesions in the right mid-ribs anterolaterally; the left side was clear.

This patient wanted a limited amount of involvement and certainly would refuse to return for numerous follow-ups or repeat procedures. She was extremely apprehensive about pain and the attempts made to assist her. After reviewing the alternative treatments, including continued narcotics with probable progression to parenteral administration, selective ablative intercostal nerve blocks and spinal narcotics, along with the expected levels of success and risk associated with each, we agreed to attempt interpleural analgesia.

With the patient in the left lateral decubitus position and carefully placing her right hand over her head, a skin wheal was made in the fifth intercostal space posteriorly at the angle of the rib after the skin was prepared. Using a 17-gauge Tuohy needle, the fifth thoracic rib was walked off superiorly and advanced into the pleural space, employing loss of resistance technique as described by Reiestad and Strömskag (1). Ten ml of bupivacaine 0.25% was instilled, and a Portex epidural catheter was inserted approximately 6 to 7 cm, the needle withdrawn, and the catheter secured in place with a nylon suture. This was covered with an occlusive plastic dressing after applying antibiotic ointment and the catheter taped up the back over the shoulder. No attempt was made to tunnel the catheter. Pain relief was almost immediate, and she was discharged soon after with the intention that the catheter would be replaced in a few days and tunneled under her skin if the temporary one proved successful. The family was given a supply of 0.25% bupivacaine along with full service instruction concerning care of the catheter, injection protocol, and recognition of side effects.

The next day she was readmitted by her private physician for nausea, vomiting, anorexia, and dehydration. Local anesthetic toxicity was the initial diagnosis. However, it was soon learned that because she felt so good from the interpleural analgesia, she abruptly halted her oral morphine. While she was hospitalized, the dose of bupivacaine was decreased to 2 ml, which still gave adequate relief lasting 4 to 6 hours. The patient was again discharged with a supply of bupivacaine and instructions to continue oral morphine.

An increase in the dose was quickly needed, and soon progressed up to 10 ml of 0.25% bupivacaine about two to three times per day, usually while awake. After 2-1/2 weeks, she was receiving four doses per day and after 3 weeks five doses per day with decreasing analgesia. Relocation of the catheter, accomplished by pulling it back 3 cm, enhanced the analgesic effect and the dose needed was diminished slightly. As her condition worsened, intravenous sites became nearly impossible to procure. Nalbuphine, which she was receiving intravenously for the discomfort secondary to metastases elsewhere in her body, was instilled through the intrapleural catheter. Almost 150 doses of nalbuphine were administered by this route over the remaining 5 weeks of her life. Not only did this prove to be efficacious, but the same dose given intravenously and interpleurally was effective. These doses were delivered interpleurally by her husband approximately every 4 hours while she was awake and in an alternating manner with

bupivacaine; the latter was dispensed to specifically relieve her right chest wall and pleural pain. The nalbuphine was given interpleurally to alleviate the discomfort of growing metastases in other separate locations. By the end of the fifth week, the patient needed 10 ml of 0.25% bupivacaine every 4 hours while awake, which sufficed until her death after 7-1/2 weeks of interpleural analgesia.

Discussion

The quality of life of a cancer patient can indeed be poor. First, they are told that they may die, but no one can tell them when with any certainty. They tolerate nausea, lethargy, malaise, depression, and last, but not least, pain. Constantly receiving intravenous and intramuscular injections, they may donate seemingly endless tubes of blood, often to no discernable benefit. Despair and depression soon dominate their lives. It behooves us as health providers not only to make their remaining time as comfortable as possible, but to accomplish that goal simply and effectively.

Although this patient had several metastases, in only one area was pain severe enough to warrant direct treatment. Irradiation to her chest helped only slightly, and systemically administered narcotics, although offering relief for other less painful areas of her body, did not significantly affect her chest pain. Possible alternative treatments included continued narcotic administration with progression to the intravenous route, destruction of two or three intercostal nerves (3), or epidural narcotics (4). Neuroablation or epidural narcotics could always be employed if the attempt at interpleural analgesia failed. This was a highly fearful and suspicious patient who we felt would only afford us one initial trial and would not tolerate side effects. Knowing that epidural morphine can initially be associated with respiratory depression, pruritus, urinary retention, or nausea and vomiting (5), interpleural analgesia appeared to be the first choice for the patient. It would also give her opiate receptors a rest in the event that epidural narcotics were required in the future for widespread pain.

Pleural fibrosis has been considered to be a relative contraindication to interpleural analgesia, both because pleural thickening may cause difficulties in identifying the pleural space, and the spread of local anesthetics in the pleural space may be diminished. Also, past failures have been attributed to pleural effusion either preventing spread or diluting the anesthetic solution. Bruce et al. (6), however, re-

ported successful results when administering interpleural analgesia for postcholecystectomy pain in a patient with cystic fibrosis. Pleural pathology, though not normally associated with, can be a result of cystic fibrosis. The patient in this report had a thoracotomy, right upper lobectomy, and chest radiotherapy. She had extensive fibrosis and pleural thickening with pleural fluid. The latter was minimal and probably had an insignificant effect on the potency of the local anesthetic. In the presence of such widespread fibrosis and tumor involvement, why the interpleural injection was still productive remains unclear. There may have been a local pocket formed by the adhesions, which still allowed the anesthetic solution to remain in its desired target area, or the catheter tip may have been fortuitously located adjacent to the involved intercostal nerves. Alternatively, pleural fibrosis may not significantly affect the quality of the block, as was previously thought. More case studies are necessary to verify this last possibility.

Previous reports of the efficacy of interpleural local anesthetics have dealt only with relatively short-lived pain, usually from postsurgical or post-traumatic causes. No catheters were employed for more than just a few days. In our case, the same catheter was utilized for a full 7-1/2 weeks until the patient's death. She remained free of infection for the duration of the catheter's employment; the insertion site was kept clean and dry. This case illustrates that long-term commitment to the management of chronic pain can be contemplated with an interpleural catheter technique.

Repositioning the catheter when the effect was diminishing restored the analgesic efficacy to its original level. This may have occurred for one of two reasons. The plastic catheter or the solution may have stimulated pleural thickening around it, which could have prevented the anesthetic solution from being freely distributed about the tip of the catheter. A similar experience occurring in the epidural space was reported by Coombs et al. (7). Second, it is possible that the catheter was simply withdrawn closer to the T4-T5 area, its desired target of action. Because no autopsy was performed, nor was the catheter radiopaque, it was difficult to ascertain which of these possibilities was more likely or how much each contributed.

After 5 weeks of interpleural analgesia, when obtaining intravenous sites became almost impossible, the interpleural catheter was utilized to administer parenteral nalbuphine. Not only was this an efficacious method of administration, but the interpleural dose of nalbuphine appeared as effective as the same dose given intravenously. The injection of other medications that may be absorbed and effective by this route should be explored, particularly when peripheral or even central intravenous access becomes difficult to obtain. Because epinephrine, lidocaine, and other drugs have been found to be efficacious when administered via endotracheal tubes in emergency situations, so might they if given via an interpleural catheter. Drugs given in this manner may also have the added benefit of reaching the left ventricle faster than if injected peripherally.

When the time came that an average of 4 hours of relief was achieved with each injection, the question arose as to whether a continuous infusion should be instituted, or when epinephrine should be added to the bupivacaine. The former was discarded because it was felt that the patient might have to lie continuously in the recumbent position for the anesthetic to bathe the T4-T6 intercostal nerves. Epinephrine, according to Denson et al. (8) and our personal experience, does not significantly prolong the duration of interpleural analgesia. Also, as is occasionally the case in many peripheral nerve blocks, absorbed epinephrine may produce undesirable tachycardia (9) or other side effects. Our patient was one who might have abandoned an otherwise profitable technique with the appearance of one undesirable side effect. Besides, she and her family were content with the 4 to 5 hours of relief as long as there were no signs of toxicity and they could reinject freely.

The improvement in the quality of life for this individual was immeasurable. It allowed her to sit up again and resume one of her favorite pastimes (knitting). However, this technique will probably not suffice for everyone. The painful lesion must be localized to the right or left chest. There should not be significant pleural effusion that would decrease the efficacy of the interpleural injection or possibly serve as a culture medium for infection. Lastly, the patient, family, or attending nurses must be willing to continue repeated interpleural injections for prolonged periods. Possibly a continuous interpleural infusion delivered by pump may be beneficial. Aside from the well-known side effects to watch for, such as infection, anesthetic toxicity, displacement of the catheter, and pneumothorax, another potential problem may be local tissue reaction around the catheter tip similar to what may happen in the epidural space, as noted by Waldman et al. (10). If that were to happen, the catheter should be withdrawn slightly or repositioned in another interspace.

Interpleural analgesia is certainly efficacious in the management of the postoperative pain of breast operations and renal surgery (1), cholecystectomy (11), and thoracotomy (12) and for fractured ribs (13) and

chronic pancreatitis (14). Now it appears to be useful not only for thoracic pain due to cancer infiltration or metastases, but also in patients with pleural fibrosis secondary to thoracotomy and lung resection, as was not previously thought possible. Where interpleurally placed catheters were up until now employed for only a few days, the same catheter served our patient for 7-1/2 weeks. As an added benefit, interpleural catheters may be useful as an alternate route of medication infusion when obtaining intravenous access becomes difficult. Although more experience with this technique is needed, it appears that extended use of interpleural injection of local anesthetic solutions is useful and that the possibility of the need for chronic administration should not be a deterrent.

References

1. Reiestad F, Strömskag KE. Interpleural catheter in the management of postoperative pain. A preliminary report. Reg Anesth 1986;11:89–91.

2. Durrani Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. Anesth Analg 1988;67:479–81.

3. Long DM. Relief of cancer pain by surgical and nerve blocking procedures. JAMA 1980;244:2759–61.

4. Poletti CE, Cohen AM, Todd DP, Ojemann RG, Sweet WH, Zervas NT. Cancer pain relieved by long-term epidural morphine with permanent indwelling systems for self-administration. J Neurosurg 1981;55:581–4.

5. Reiz S, Westberg M. Side-effects of epidural morphine (letter). Lancet 1980;2:203–4.

6. Bruce DL, Gerken MV, Lyon GD. Postcholecystectomy pain relief by intrapleural bupivacaine in patients with cystic fibrosis. Anesth Analg 1987;66:1187–9.

7. Coombs DW, Fratkin JD, Meier FA, Nierenberg DW, Saunders RL. Neuropathologic lesions and CSF morphine concentrations during chronic continuous intraspinal morphine infusion: a clinical and post-mortem study. Pain 1985;22:337–51.

8. Denson D, Sehlhorst CS, Schultz REG, Gregg RV, Bridenbaugh PO, Grummich KW. Pharmacokinetics of intrapleural bupivacaine: effects of epinephrine. Reg Anesth (Suppl) 1988; 13:47.

9. Kennedy WF Jr, Bonica JJ, Ward RJ, Tolas AG, Martin WE, Grinstein A. Cardiorespiratory effects of epinephrine when used in regional anaesthesia. Acta Anaesthesiol Scand 1966;23: 320–33.

10. Waldman SD, Feldstein GS, Allen ML. A troubleshooting guide to subcutaneous epidural implantable reservoir. J Pain Symptom Manage 1986;1:217–22.

11. Brismar B, Pettersson N, Tokics L, Strandberg A, Hedenstierna G. Postoperative analgesia with intrapleural administration of bupivacaine-adrenaline. Acta Anaesthesiol Scand 1987;31:515–20.

12. Rosenberg PH, Scheinin BMA, Lepäntalo MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 1987;67:811–3.

13. Rocco A, Reiestad F, Gudman J, McKay W. Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures: a preliminary report. Reg Anesth 1986;12:10–4.

14. Sihota MK, Holmblad BR, Ikuta PT, Candido KD. Successful pain management of chronic pancreatitis patients with intrapleural technique. Reg Anesth (Suppl) 1988;13:33.

Letters to the Editor

Rebreathing Affects Deadspace Measurements Using the Siemens-Elema 930 CO_2 Analyzer

To the Editor:

Dr. Fletcher presents an excellent discussion of respiratory deadspace in anesthetized children with cardiac disease (1). However, he does not caution against an error that may occur when using the Siemens-Elema 930 CO_2 analyzer. The design of this analyzer is such that it always assumes that there is no rebreathing of expired gases (2). The inspired gases are taken as the reference against which to measure the CO_2 concentration in the expired gases. If rebreathing occurs, the 930 analyzer will indicate that end-tidal CO_2 is lower than it actually is. We observed rebreathing measured by mass spectrometry in infants and children ventilated with a Siemens-Elema 900-C Servo when inspiratory:expiratory ratios (I:E) were ≤1:3.5 (i.e., 1:4, 1:5, 1:6) (3). Therefore, if rebreathing occurred in Dr. Fletcher's patients, the $PaCO_2$ − $P_{ET}CO_2$ gradient would be inaccurate and non-invasive measurement of respiratory deadspace would be affected.

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References

1. Fletcher, R. Invasive and non-invasive measurement of the respiratory deadspace in anesthetized children with cardiac disease. Anesth Analg 1988;67:442-7.

2. Olsson SG, Fletcher R, Jonson B, Nordstrom L, Prakash O. Clinical studies of gas exchange during ventilatory support—a method using the Siemens-Elema CO_2 analyzer. Br J Anaesth 1980;52:491-9.

3. Badgwell JM, Heavner JE, May WS, Goldthorn JF, Lerman J. End-tidal PCO_2 monitoring in infants and children ventilated with either a partial rebreathing or a non-rebreathing circuit. Anesthesiology 1987;66:405-10.

In Response:

I thank the Editor for the invitation to reply to the comments of Drs. Badgwell and Heavner concerning my paper (1) on the respiratory deadspace in anesthetized children. It is true that, for the sake of simplicity, the paper did not mention the rebreathing of expired gases. However, this phenomenon was discussed at some length in the previous paper (2), to which the reader was referred for methodological details.

Reference (2) described, in its methods section, two validation experiments designed to demonstrate the accuracy of both the Siemens-Elema CO_2 Analyzer 930 alone, and of the on-line computerised system *in toto*. It was shown that, compared to readings obtained at tidal volumes of 0.5 1, there was an underestimate of about 1% at a tidal volume of 200 ml, 2% at 150 ml, 3% at 100 ml, and 5% at 50 ml. The CO_2 analyzer alone and the on-line system produced the same magnitude of error, so it was assumed that this error stemmed from the design of the CO_2 analyzer. The probable explanation is that the CO_2 transducer takes a new zero during each inspiration. Small inspiratory tidal volumes do not totally clear the measuring cuvette of CO_2 during inspiration. "The CO_2 signal is logarithmic and is not linearized until after the new zero is registered. Because of this effect, the zero error is grossly out of proportion to the number of CO_2 molecules present" (2).

In my paper (1), the tidal volume dependent error was corrected for in the calculation of $V_D$phys and $PaCO_2$ − $P_{ET}CO_2$. (It is not necessary for the measurement of V_DBohr). The smallest tidal volume used in the children presented was 50 ml (some children with smaller tidal volumes in paper (1) were omitted). Thus the findings presented should represent a "best estimate" of deadspace values under ideal conditions. As Badgwell and Heavner suggest, considerably worse estimates will be obtained when less suitable equipment is used, or if no correction is applied.

It is possible to quantify the rebreathing to some extent. My colleague Drefeldt observed the primary signal of the CO_2 Analyzer on an oscilloscope. Even at tidal volumes of 50–100 ml, the CO_2 signal decreased rapidly during early inspiration, later roughly exponentially. It is thus minimal at the end of inspiration, when a new zero is taken. We know from my colleague Werner's isotope studies similar to those performed in adults (3), that the total rebreathed volume is equivalent to about 3 ml of endtidal gas. At a $P_{ET}CO_2$ of 5 kPa (38 mm Hg) this gives 0.15 ml CO_2. Even if this were evenly spread over the whole inspiration it would give a P_ICO_2 of 0.3 kPa (2 mm Hg) at 50 ml tidal

volume and 0.15 kPa (1 mm Hg) at 100 ml. However, since the oscilloscope study showed that most of the rebreathed CO_2 is aspirated at the beginning of inspiration, the P_ICO_2 at the time of the establishment of the new zero will be orders of magnitude less. (But as we have seen, this is enough to influence the zero somewhat).

It is interesting to compare the P_ICO_2 values measured by Badgwell et al. (4) with the above. In their sampling system, 240 ml of gas was aspirated per minute to a mass spectrometer from the connecting tube. Figure 4 in their paper, obtained at a frequency of 28 bpm, tidal volume 48 ml, shows that PCO_2 falls only slowly during expiration, and reaches a minimum of 3 mm Hg; true zero is not reached at any stage. The only reasonable explanation for the discrepancy between their results and ours is that mass spectrometer sampling from the connecting tube of a pediatric circuit affects what is being measured. It therefore cannot tell us what is going on in an in-line sampling system. In other words, the system used by Badgwell et al. is probably unsuitable for pediatric anesthesia, and gives results which may not be extrapolated to other systems. My own feeling is that the known 5% error in measurement at tidal volumes of 50 ml with the Siemens-Elema system is acceptable in clinical practice: for scientific purposes a correction should be applied. One can hope that new studies quantifying the performance of other pediatric CO_2 monitoring systems will be published in the near future.

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References

1. Fletcher R. Invasive and noninvasive measurement of the respiratory deadspace in anesthetized children with cardiac disease. Anesth Analg 1988;67:442–7.

2. Fletcher R, Niklason L, Drefeldt B. Gas exchange during controlled ventilation children with normal and abnormal pulmonary circulation: a study using the single breath test for carbon dioxide. Anesth Analg 1986;65:645–52.

3. Fletcher R, Werner O, Nordström L, Jonson B. Sources of error and their correction in the measurement of carbon dioxide elimination with the Siemens-Elema CO_2 Analyzer. Br J Anaesth 1983;55:177–85.

4. Badgwell JM, Heavner JE, May WS, Goldthorn JF, Lerman J. End-tidal PCO_2 monitory in infants and children ventilated with either a partial rebreathing or a non-rebreathing circuit. Anesthesiology 1987;66:405–10.

A Modified Stretcher-Lifter Device for Transfer of Patients during Extra Corporeal Shock Wave Lithotripsy (ESWL)

To the Editor:

The Dornier HM-3 lithotripter, currently the most commonly employed machine in the United States for fragmentation of urinary tract stones, requires that patients be positioned in a gantry chair and then immersed in a water bath. During general anesthesia for lithotripsy, the anesthetized patient is transferred from a stretcher to the gantry
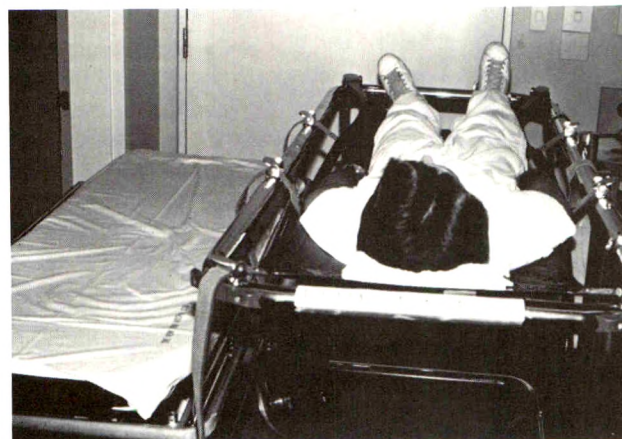
Figure 1. The Surgilift Stretcher-Lifter with a volunteer lying on the mat which is attached to the frame with straps. The crank-handle with the black knob on the right moves the top of the frame vertically up or down.
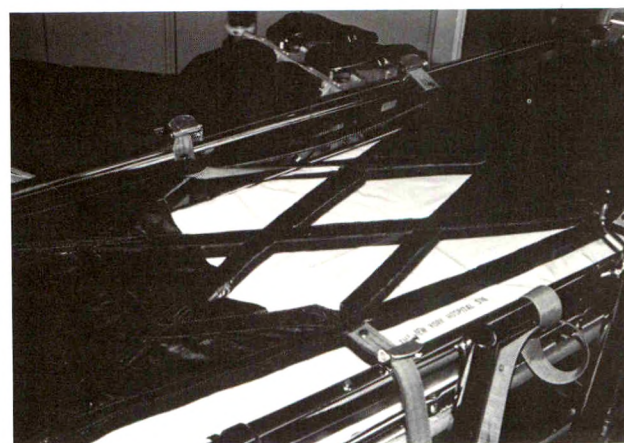
Figure 2. Photograph showing the black mat with the windows where the patient's flank area would lie.

chair at the beginning, and vice versa at the end of the treatment. The sudden lifting movements of the anesthetized patient places him at risk of impact injury against metal parts of the gantry chair or the stretcher. Lifting heavy patients in such a manner places ESWL personnel at risk of low back strain. To facilitate this transfer without manually lifting patients, we use a commercially available stretcher-lifter device with a simple modification as described below.

The Surgilift Stretcher-Lifter (Trans-Aid Corporation, Carson, CA 90740, Maximum Capacity 400 lbs), commonly used to transport patients, consists of a metal frame on wheels which can be positioned over the operating table or the patient's bed. The patient lies supine on a mat with heavy straps sewn criss-cross onto it. The patient's weight is supported by these straps which are secured in the buckles on the frame. With the mat secured, the frame can be raised or lowered using a crank handle, allowing patient transport without manual lifting (Fig. 1).

We modified the mat for ESWL use by cutting out windows in the mat in the flank area while leaving the

supporting straps intact (Fig. 2). This allows uninterrupted propagation of the shock waves to the entry site in the flank. The patient is still firmly supported by the heavy criss-cross straps, which are carefully kept clear of the shock wave entry site.

Patients anesthetized on a stretcher or a cystoscopy table, are transferred to the gantry chair with ease. The stretcher-lifter is carefully lowered onto the gantry chair and the straps slowly released one at a time as the patient gently settles in the gantry chair. The mat stays under the patient during lithotripsy. At the end of the procedure, the Surgilift® frame is lowered onto the gantry chair as the mat is reattached to it. The patient is then gently raised, using the crank handle on the Surgilift® and transferred to a stretcher.

The sudden, jerky movements associated with manual lifting of patients are minimized by the use of this device. In addition, no heavy lifting is required of the ESWL personnel. We have used it with success in approximately 700 patients (body weight range 40 kg to 135 kg) undergoing ESWL at our institution and find it to be safe, convenient and reliable.

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Figure 1. Transverse section. Needle puncturing anterior wall of IJV. Curved arrows—internal and external carotid arteries. Straight arrow—needle.

Real-Time Ultrasound Imaging Aids Jugular Venipuncture

To the Editor:

We were interested in the description by Fukutome at al. (1) of subclavian venipuncture using a Doppler probe. Our particular interest has been in the cannulation of the internal jugular vein (IJV) in difficult situations such as subcutaneous emphysema or scarring from previous neck surgery. Defalque validated the reliability of the anatomical landmarks in the neck for this procedure in normal patients (2). Studies have been published supporting the accuracy of ultrasonographic anatomy of the IJV but have only described localization (3–6). Cannulation was subsequently performed without ultrasonographic aid. Our objective was to obtain real-time imaging of the relationships between the advancing needle and structures in the neck.

We found that a small linear array transducer was better than larger linear array or small sector scanners with lower frequency. Our final choice was a Siemens Sonoline SL2 ultrasound unit with a 7.5 MHz linear array transducer with dynamic focussing. This allowed focussing at different depths. The size of the footpad in contact with the skin was 5 × 1.5 cm. This transducer also provided the advantages of intermittent pulsed Doppler permitting detection of clot filling the lumen of a vein selected for cannulation. Following skin preparation and gel application, the transducer was placed inside a sterile plastic sheath containing gel. The transducer was applied to the skin and aligned in the transverse axis to the vascular structures just caudad to the
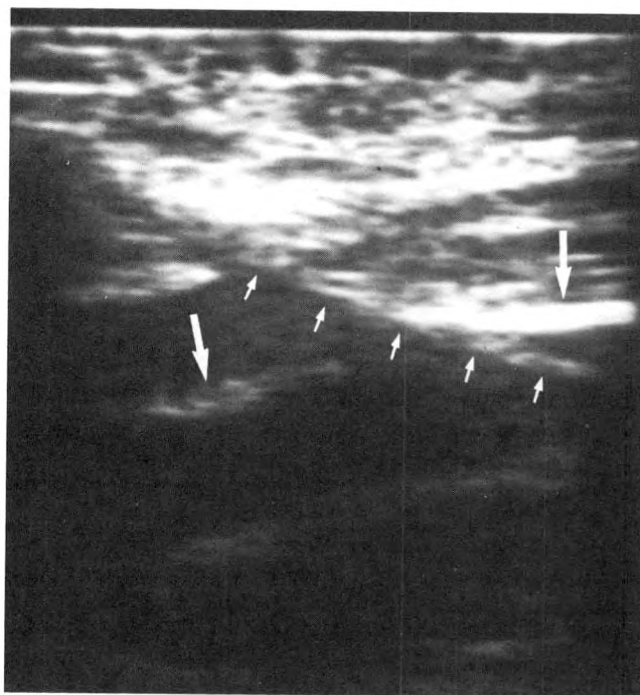
Figure 2. Sagittal section. The small arrows show the needle in the soft tissue, as it passes through the anterior vein wall and into the lumen of the vein. Large arrows—anterior vein wall.

skin puncture site. Under real-time visualization, the advancing needle could be seen as it passed through the tissues of the neck and the vein wall. This imaging indicated necessary adjustments in the direction and depth of the needle to facilitate satisfactory cannulation. Figure 1

shows the needle as it punctures the anterior wall of the IJV. Figure 2 is a sagittal section of the neck showing the needle passing through the anterior vein wall and lying in the lumen of the vein.

This technique provides greater safety in cannulating the IJV in patients in whom the usually reliable anatomical landmarks are distorted.

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References

1. Fukutome T, Tanigawa K, Fukunaga AF. Subclavian venipuncture: a new device using a Doppler probe. Anesth Analg 1987;66:1338–9.
2. Defalque RJ. Percutaneous catheterization of the internal jugular vein. Anesth Analg 1974;53:116–21.
3. Bazaral M, Harlan S. Ultrasonographic anatomy of the internal jugular vein relevant to percutaneous cannulation. Crit Care Med 1981;9:307–10.
4. Tryba M, Kleine P, Zenz M. Sonographic studies for optimizing the cannulation of the internal jugular vein. Anaesthesist 1982;31:626–9.
5. Legler D, Nugent M. Doppler localization of the internal jugular vein facilitates central venous cannulation. Anesthesiology 1984;60:481–2.
6. Ullman JI, Stoelting RK. Internal jugular vein location with the ultrasound Doppler blood flow detector. Anesth Analg 1978;57:118.

Suction Catheter to Facilitate Blind Nasal Intubation

To the Editor:

The letter to the editor from Williamson commenting on an article by Baraka and Baraka's reply (1) bemoaning the general decline of skills at blind nasal intubation, struck a sympathetic chord. Cases arise in which neither oral laryngoscopic nor fiberoptic intubation are possible. Routine maneuvers of nasal intubation have been well described (2). As an addition to this field, I have employed a suction catheter as a guide to facilitate blind nasal intubation.

In one case, an 83-year-old female with an hiatal hernia and frequent, massive reflux of gastric contents required general anesthesia for a gastrostomy. She would not open her mouth for examination. Blind nasal intubation repeatedly failed while copious gastric fluid, which would have blinded a fiberscope, issued from the endotracheal tube. The tip of the tracheal tube was withdrawn into the nasopharynx; through the tube, an ordinary, flexible 14 French suction catheter was passed into the trachea. With a few twists of the tracheal tube and flexion of the neck, the tube followed.

An 88-year-old male with cervical spondylosis, refusing to open his mouth, was scheduled for a gastrostomy. Epistaxis began during attempts to apply local anesthetic/vasoconstrictor. Unable to manipulate the head and neck, several tries at blind nasal intubation failed. A 14 French suction catheter, passed through the tracheal tube, entered the trachea and provided a guide for intubation.

A 94-year-old female was scheduled for gastrostomy and refused to open her mouth for examination. Despite the application of a local anesthetic/vasoconstrictor, gentle passage of a tracheal tube through either nasal passage was not possible. A warmed, lubricated 14 French suction catheter through the tracheal tube negotiated the bend into the nasopharynx and trachea and provided a guide for the passage of the tube.

Smaller than the endotracheal tube, a suction catheter can slip into the trachea, reducing the task to one of timing the tube's passage through the vocal cords, instead of the dual challenge of aiming the tube at the glottis while simultaneously timing its passage. Additionally, the soft catheter can guide a tracheal tube through a tight nasal passage, preventing epistaxis and submucosal dissection.

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References

1. Williamson R. Endotracheal intubation in temporomandibular ankylosis. Anesth Analg 1988;67:602–603.
2. Finucane BT, Santora AH. Principles of Airway Management. Philadelphia: F. A. Davis, 1988:142–143.

Effect of Transparent Adhesive Tape on Pulse Oximetry

To the Editor:

I read with interest the recent article (1) on the effect of nail polish on the performance of pulse oximeters. Further to this, and previous work (2,3) on the effects of dyes and other colorants, may I describe the investigations I have recently carried out on the effect of the presence of transparent or translucent adhesive tape on pulse oximetry?

My interest in this was aroused when I noticed two facts of theatre life: (a) the oximeter probe is usually placed on the arm that does not have the blood pressure (B.P.) cuff on it; and (b) the B.P. cuff is usually placed on the arm that does not have the intravenous cannula in it. Thus there is the possibility that part of the tape holding the cannula in place may lie in the path of the infra-red beam of the oximeter, especially in children or babies.

A closed circle re-breathing system was set up using a soda-lime absorber, and this was flushed through with air. Using this system it was possible to partially desaturate the blood of the subject (the author) in a slow and controlled manner down to a level of 85%.

To date, six types of tape have been tested using two different makes of pulse oximeter, namely the Kontron (Kontron Instruments Ltd., Watford, England), and the Novametrix (Medical Systems Inc., Wallingford, Connecticut, U.S.A.).

The following adhesive dressings were tested:

Blenderm (3M)
Dermilite (3M)

Durapore (3M)
Micropore (3M)
Bioclusive (sterile) (Johnson and Johnson)
Opsite (Smith & Nephew Medical Ltd, Hull, England)

On each test two of each type of oximeter were used. The probe from one (the control machine) was placed on a finger of the left hand that was untaped. The probe from the other oximeter (the test machine) was placed on an untaped finger to confirm that the two machines read the same value. The subject then rebreathed through the circle system and note was taken of any difference in the readings of the two machines as the control reading slowly dropped to 85%.

Another finger of the same hand was enwrapped with one layer of tape so that the beam of the test machine passed through the tape twice, once on each side of the finger, and the subject rebreathed again to allow the arterial saturation to fall to 85%. Any difference greater than 1% between the readings of the two machines was noted.

This regimen was repeated using all six types of tape and then using both makes of machine.

Some differences were noticed in the times that the reading changed, on the machines (despite being set on the same averaging time). This was true even when the test machine was on an untaped finger.

No consistent differences in the readings of the test and control machines were seen in any combination of machine type or tape. Thus the combinations of tape and machine described here appear to be safe to use in the clinical setting. It behooves the clinician using an oximeter through any other combination of tape and machine to check, either by experiment or by consulting the relevant manufacturers, that the readings are accurate and reliable at full saturation and also at partial saturation.

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References

1. Coté CJ, Goldstein EA, Fuchsman WH, Hoaglin DC. The effect of nail polish on pulse oximetry. Anesth Analg 1988;67:683–6.
2. Kataria BK, Lampkins R. Nail polish does not affect pulse oximeter saturation. Anesth Analg 1986;65:824.
3. Scheller MS, Unger RJ, Kelner MJ. Effects of intravenously administered dyes on pulse oximetry readings. Anesthesiology 1986;65:550–2.

Major Thoracic Incisional Injury: Ventilatory Management

To the Editor:

A 23-year-old, previously healthy male, weighing about 60 kg, was admitted after a single 30-cm long machete injury to his right chest wall extending from the right of the sternum at the level of T-6 toward the mid axillary line. The lung was not visible. He was fully conscious, his pulse rate regular at 64 beats/min; his blood pressure was 120/70 mm Hg and hemoglobin 10.5 g%. An intercostal drain was immediately inserted and was correctly placed as seen by the water meniscus in the glass tube in the underwater seal bottle moving up and down with respiration. A great deal of froth was also noted in the bottle. Twenty minutes later, general anesthesia was induced with use of etomidate followed by succinylcholine 100 mg, and a left double lumen tube was passed into the trachea. The double lumen tube was used because of the clinical suspicion of a broncho-pleural fistula. Initially, both lungs were ventilated, but the patient immediately became cyanotic. Therefore, the right lumen of the double lumen tube ventilating the right lung was occluded by a clamp at the mouth end leaving only the left lung to be ventilated. The patient's color improved, and the now in place oximeter showed the oxygen saturation to be 92%. An arterial blood sample had a PaO_2 of 11.7 kPa (88 mm Hg). At operation, a large, single laceration of the lung, a 15-cm laceration of the diaphragm, and a 5-cm laceration of the liver were found.

The diaphragm was repaired and the lung expanded adequately, but there was still considerable froth in the chest drain. The chest was closed and the patient transferred to the intensive care unit with the double lumen tube in situ. In the intensive care unit, both lungs were initially ventilated, but because both PaO_2 and oxygen saturation again fell, the left lung only was once again ventilated. Oxygen saturation and PaO_2 returned to normal levels within minutes. Chest x-ray film confirmed the correct placement of the double lumen tube. The patient remained stable throughout the next 10 hours and was extubated the next morning. His color was good, and his PaO_2 was 12.67 kPa (95 mm Hg) while breathing spontaneously (FIO_2 28%). Three days later, he was sitting up in bed, the chest drain removed and the chest x-ray film normal. We do not believe that this patient had a broncho-pleural fistula but, more likely, had hundreds of secondary and tertiary broncheoles cut, causing a clinical picture similar to that seen with a broncho-pleural fistula.

We call attention to this case because in a traumatic incisional type of injury, cutting through parenchymal pulmonary tissue, a situation may result comparable with that seen in a patient with a broncho-pleural fistula. In this case, however, considerable frothing occurred unlike a case in which a broncho-pleural fistula occurs.

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Book Reviews

Pocket Manual of Anesthesia

G. Lenz, B. Koller, R. Schorer and W.E. Spoerel.
Philadelphia: Decker, 1988, 318 pp, $18.50.

The Pocket Manual of Anesthesia is both conceptually and physically designed to be a compendium of "facts, data, and knowledge relevant to daily practice in a format which, by fitting into the pocket of an operating room gown, (makes) it available at work." The manual was originally published in 1985 in German and translated into English in 1988. With this cosmopolitan background, the manual displays many of the advantages and a few of the disadvantages of texts written for foreign audiences. Those recommendations and assumptions which are true both to German and North American anesthetic practice must be nearly universal truths; there are, however, significant regional differences in practice and pharmacopeia which are evident throughout this book and prevent its uncritical acceptance.

The manual is logically organized into brief, readily assimilated chapters on the fundamental topics and skills involved in most anesthetics: premedication, arterial and venous cannulation, inhalational and injectable anesthetics, regional anesthesia, etc. There are three chapters which come at the end of the text dealing with "Special Situations," "Complications" and "Anesthesia-Related Problems." The first is an ambitious, alphabetical treatment of a variety of challenges confronted by the anesthesiologist in his or her practice, such as diabetes, burns, obstetrics, the full stomach etc. Despite its scope, this chapter serves as an efficient reminder of the salient issues in managing each of these situations. The chapter on complications covers such topics as air embolism, difficult intubations, anaphylactic and hemolytic reactions, malignant hyperthermia and aspiration from both the diagnostic and management standpoint. The final chapter, on anesthesia related problems, is a by no means exhaustive treatise on anesthesia and comorbid conditions, which is useful in those areas which it covers, but somewhat capricious in covering hyperkalemia and not hypokalemia. Relatively obscure disease such as acromegaly, adrenogenital syndrome and thalassemia are mentioned while equally or more common diseases such as chronic obstructive pulmonary disease are overlooked.

Many of the tables and diagrams are quite useful and extracted unapologetically from the world's literature. There are some inconsistencies in drug dosage recommendations, wherein some drugs are dosed as for a seventy kilogram man: for antihistamines "1 to 2 ampules slowly IV (for allergic reactions)," others are given in mg/kg doses, and infusions merit extensive and sometimes confusing two part tables. There are many references to drugs unavailable to or infrequently used by American anesthetists, such as propafenon, flunitrazepam and intravenous clonidine, which are actually tantalizing as some of these drugs will certainly find their way into North American practice.

One specific problem with this manual and perhaps with its European derivation lies in certain recommendations regarding perioperative and intraoperative management which conflict with American practice. The recommendation that oral contraceptives be discontinued several weeks before surgery to prevent thromboembolism conflicts with common practice in this country, and would, undoubtedly, meet with resistance in our patient population. Similarly, enflurane is felt to be contraindicated with the simultaneous use of beta blockers for fear of profound hypotension, a problem not generally recognized here. Presumably these are examples of ways in which European management differs from our own, and in no way invalidates such management; but the reader must be cautious in accepting all of the authors' recommendations blindly.

With the aforementioned reservations, I found *The Pocket Manual of Anesthesia* to be a useful, concise and generally informative adjunct to the day to day practice of anesthesia—a text any anesthesia resident, nurse anesthetist or practicing anesthesiologist might want to carry on or near his person while in the O.R. The authors are to be complimented on their ability to compress the acceptable minimum amount of information from this complicated field into an easily read, easily carried format.

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Anesthesia in Hepatic and Biliary Tract Disease

Burnell R. Brown, JR. Philadelphia: FA Davis Co., 1988, 300 pp, $58.00.

This book, which comprehensively deals with all aspects of the liver from the anesthesiologist's perspective, fills a void in our discipline's literature.

The book is somewhat arbitrarily divided into five sections: i) Fundamental Principles in which there are chapters addressing the anatomy, physiology, circulation and measurement of liver function; ii) Anesthetic effects on liver

circulation and function encompassing four chapters including one on hepatotoxicity; iii) Liver Disease and the Anesthesiologist, a catchall section addressing the clinical manifestations of liver disease and anesthetic considerations of the same; iv) Biliary Tract Disease comprising a single chapter dealing with physiology, pathophysiology and anesthetic management of patients with extrahepatic biliary obstruction; and v) a Special Problems section dealing with postoperative liver dysfunction and the liver diseases and anesthetic management which is peculiar to the pediatric population. This being a single author book, better organization of the wealth of material that is presented was expected. For example, it would have made more sense to divide the book into Physiology, and Pathology sections and deal with the anesthetic effects and implications respectively of these two broad categories. This would preclude the inconsistency of placing liver circulation and anesthetic effects on hepatic circulation material in two separate sections while anesthetic effects on drug biotransformation follows more appropriately immediately after drug biotransformation reactions.

Within each of the chapters, a list of contents precedes the narrative and the author employs tables or "boxes" in which to list the most salient facts. These devices should prove quite useful as an index and a ready reckoner, respectively, for the casual reader. However the pithy boxes are sometimes meaningless by themselves, e.g., Table 5-4, in which the direction of alteration, perhaps with arrows, would transform the data on factors altering hepatic blood flow into selfsufficiency.

The author has his own inimitable style which converts bland facts into racy prose. He also colors the text with provocative and dogmatic statements which, in my opinion, is justified based on the author's stature in this field. A number of typographical errors detract from the author's efforts and should have been spotted by the editorial assistant.

There are some chapters, notably those on Drug Biotransformation by the Liver, Hepatotoxicity of Inhalation Anesthetics and Postoperative Jaundice which are authoritative, up to date and very well referenced. These clearly reflect the author's leadership role in these areas. Alas, there are others in which the author is not current and it shows by the inclusion of a majority of references that are 15 years or older. Alternatively, the author could have solicited the help of another scribe which would have compromised the obvious virtues of a single-author tome.

On balance, I enjoyed reading this book which is so obviously a labor of love written by an expert in the field. This should be a must in any well-stocked anesthesia library whether it be in an institution or in a private dwelling.

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Consciousness, Awareness, and Pain in General Anaesthesia

Edited by M. Rosen and J. N. Lunn, Boston, Butterworths, 1987, 195 pp, $34.95.

Ever since the first demonstration of general anesthesia at Massachusetts General Hospital on October 16, 1846, the problem of awareness and recall during surgery has been of practical and philosophical interest to anesthesiologists. The apparent random occurrence of the recall of intraoperative events has led to many studies attempting to define the conditions under which awareness and recall occur. Other work has attempted to describe the phenomenology of perioperative awareness as well as the postoperative sequelae of such events. The medicolegal aspects of consciousness, awareness, and recall have been of more recent interest. It has become apparent that here is a spectrum of awareness phenomena. These include: responsiveness to intraoperative stimulation (surgical and nonsurgical), awareness without postoperative recall, actual postoperative recall, recall that could be elicited under special circumstances such as hypnosis, and recall that manifests itself in attitudes, emotions, and behaviors without the apparent presence of verbal memory. The problem that has faced the clinician has been that of knowing how to identify the presence of awareness and recall objectively. The best indicators have, until now, been clinical signs. Among the most important of these are blood pressure, pulse, sweating, and epiphora. The universal use of muscle relaxants has sometimes deprived the anesthesiologist of the most reliable clinical manifestation of awareness: patient movement in response to stimulation. Even this sign, of course, is only an indication that awareness might be present. There are no indicators that predict awareness and recall with absolute certainty.

Consciousness, Awareness, and Pain in General Anesthesia, is the product of a workshop held in Cardiff, Wales in June, 1986. In twenty-three well considered chapters by acknowledged experts in the field, the scope of the problem is defined and current research is described. Important data is presented on the yet nascent efforts to find objective physiological concomitants to awareness and recall. Attempts to predict and abort awareness using electromyographic and electroencephalographic techniques are described in some detail. The problems faced in attaining objective measures of subjective states of consciousness are brought into focus and the directions of future research are defined. Medicolegal issues are presented as they affect medical practice in both the United Kingdom and the United States.

This volume presents the most complete assessment of the problem of awareness and recall that has been published to date. The articles are thought provoking. The reader is challenged at every turn to consider the nature of consciousness, communication, and the meaning of remembering and awareness as it is reflected in clinical practice.

If there is one shortcoming in this presentation, it is the absence of a complete discussion of the psychological effects of awareness and recall on the patient. In an appen-

dix to this work, Dr. J. M. Evans presents the verbatim descriptions of twenty-seven patients who experienced awareness and recall. The patients' descriptions of their suffering, uncertainty, and anger are compelling. Much more might have been said concerning the psychiatric implications of these experiences. Perhaps, if these patients had been interviewed by a psychiatrist, additional meaningful data would have been collected.

Human behavior, emotion, and cognition are products of previous experience. The effects on the lives of people of the experience of awareness during surgery are not given more than a cursory mention. The problem of what makes awareness and recall traumatic is not discussed. Methods of treating the patient who has been traumatized by awareness, either consciously or unconsciously, are not detailed. Little consideration is given to those circumstances in which the presence of awareness and recall might be beneficial. Nor are the effect and meaning of the lack of awareness during surgery presented. In the search for objectivity the study of the subjective itself is given short-shrift.

The publication of this volume represents an acknowledgement of how little we really understand about what we as anesthesiologists do to patients. It is a noble beginning and warrants the attention of all anesthesiologists. In an indirect way it exhorts us to consider the interface between the technical and the psychological aspects of our work. It presents a new pathway of approaching the mind/body problem. This volume is necessary reading for any anesthesiologist willing to face how much closer we stand to ignorance than to understanding. It intimates the richness of the discoveries we have yet to make.

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Controversies in Cardiovascular Anesthesia

P. Fyman, A. W. Gotta, Boston: Kluwer Academic Publishers, 1988, 192 pp, $65.00.

Much of what's taken for knowledge in medicine is open to reasonable doubt. Therefore, physicians often put pen to paper with the hope of dispelling these uncertainties. The value of books written to stimulate controversy, is that the reader must also argue with the authors' assertions, and he likewise is forced to make judgments and develop confidence in his own critical ability. To this end, "Controversies in Cardiovascular Anesthesia" is a successful book.

Five controversial topics have been chosen by the authors. The subject, inhalation versus intravenous techniques for coronary artery bypass grafting, has been debated ad nauseam for many years. Unfortunately, in this book neither side seemed enthusiastically convinced that their way is best. Both sides, however, present good reviews of the subject.

The sections for and against temperature correction of blood gases during hypothermia is excellent, and these authors speak out strongly for their position. The chapters on high versus low flow cardiopulmonary bypass, are presented mostly as textbook chapters, rather than as arguments for debate.

The final chapters consider the routine use of the pulmonary artery catheter for coronary artery bypass grafting, and regional versus general anesthesia for carotid endarterectomy. Again, the authors hesitate to take a strong stand.

Overall, the book is quite informative, but it could have been enlivened if some of the authors wrote with more conviction.

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Experimental Malignant Hyperthermia

Charles H. Williams. New York: Springer-Verlag, 1988, 166 pp, $45.00.

It is almost 30 years since Denborough published the first reports of malignant hyperthermia (MH), yet the understanding of the mechanisms responsible for this hypermetabolic hyperthermic syndrome remain poorly understood.

One of the most controversial questions concerns the role of the sympathetic nervous system. There is little doubt that in the swine model of MH, "fight, fright, or flight" can initiate an MH episode without anesthetic agents. It is also well known that during an MH episode plasma catecholamines increase markedly. Lastly, there is data from English investigators showing that alpha agonists (phenylephrine) can trigger an MH episode in susceptible swine, and that sympathetic nervous system antagonists protect or at least attenuate clinical episodes of MH. The conventional viewpoint articulated by Gronert (1) states that the involvement of the sympathetic nervous system is a secondary phenomenon and that the primary abnormality resides in skeletal muscle. Dr. Charles Williams, the editor of this book on experimental hyperthermia, has been at the center of this controversy for nearly two decades and is one of the leading proponents of the hypothesis that a massive release of catecholamines initiate the shift in metabolism which eventually results in accelerated heart production, lactic acidosis, and glycogenolysis.

The first seven chapters have been written by Dr. Williams and associates and serve to present his views on the pathophysiology of MH. References to the work of those with opposing views are used sparingly, thus a reader who is unfamiliar with how strongly Dr. Williams feels about the role of the sympathetic nervous system could receive a one-sided view of the controversy.

The majority of the book is well-written and informative, but some areas would have benefitted from more aggres-

sive editorial work, a better review of the literature, and more exact listing of the facts. For example in the chapter on plasma catecholamines during MH Dr. Williams' statement that "in 1973 the only analytic method available for catecholamines was the trihydroxyindole procedure," is incorrect. The enzymatic catechol-O-methyltransferase (COMT) assay was developed in the early 1960's by Dr. Axelrod and was available in many laboratories in 1973. The clinical studies and some of the excellent reviews appear to be the strongest portions of the book, however, they compose a small portion of the collection.

In summary, this book is an interesting review on MH by several investigators in the field. It covers a broad spectrum of MH topics including studies in man, pig, dog, and horse. The existing literature on MH needs a book like this with its expression of divergent and controversial ideas on the pathogenesis of MH. However, this book is weakened since these theories are not always presented in proper context of the work of others in the field.

Reference

1. Gronert GA. Malignant hyperthermia. In: Anesthesia. 2nd Edition, Volume 3. Miller RD (Ed.). New York, Chruchill Livingston, 1986, pp 1971–1994.

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Intravenous Anesthesia and Analgesia

G. Corssen, J. G. Reves, and T. H. Stanley. Philadelphia: Lea & Febiger, 1987, 334 pp, $48.50.

This book presents a masterly and comprehensive summary of the latest knowledge in the field of intravenous anesthesia and analgesia. Classics in this area, such as the books by C. Adams, J. W. Dundee and G. M. Wyant are already more than 20 years old and this book provides a comprehensive survey of the currently available intravenous agents and the latest techniques used to maintain anesthesia and analgesia during surgery with these agents. Having both a broad and detailed approach this book succeeds in addressing anesthesiologists, nurse anesthetists, surgeons, general practitioners, dentists, and medical students, both for general facts and for detailed information about the safe and effective parenteral use of hypnotics, tranquilizers, anesthetics, and analgesics in performing diagnostic or therapeutic procedures.

The history and evolution of intravenous anesthesia is well covered, with additional historical details specific for each drug. The various chapters include the history, chemistry, pharmacology, pharmacokinetics and metabolism of narcotics, plus chapters on barbiturates, dissociative anesthesia, neuroleptanalgesia and neuroleptanesthesia, the benzodiazepines and other specific intravenous anesthetic agents. Particular emphasis is given to short-acting powerful analgesics (such as fentanyl and its derivatives sufentanil and alfentanil) including suggestions for clinical applications. Ketamine occupies a major place due to its significance for use in patients with cardiovascular impairment, especially in the elderly, patients at high-risk, and emergency situations.

For anyone interested in the proper use of barbiturates and non-barbiturates, dissociative and neuroleptic analgesic and narcotic drugs this volume will be an excellent guide. Together with an extensive bibliography, tables, figures, and photographs this book should become another milestone in anesthesia literature and certainly fulfill its aims in making an important and timely contribution to the speciality of anesthesiology.

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Books Received

Errata

The price of *Malignant Hyperthermia* edited by B. Britt and published by Martinus Nijhoff Publishing in the September issue was incorrectly stated. The price is $69.95.

The price of *Persistent Pain, Psychosocial Assessment and Intervention* edited by N.T. Lynch and S.V. Vasudevan and published by Kluwer Academic Publishers in the March issue was inadvertently misquoted. The correct price is $69.95.

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Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

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Anesthesia and Analgesia

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1989 AWARDS

At the IARS 63rd Congress in March 1989, the Board of Trustees announced recipients of the 1989 Award as follows:

Evan D. Kharasch, MD, PhD, University of Washington School of Medicine, Seattle, WA:
"Human Endogenous Morphine and Codeine: Isolation, Mechanism of Synthesis, and Response to the Stress of Labor"

Bruce J. Leone, MD, Duke University School of Medicine, Durham, NC:
"Effects of Anesthesia on the Threshold of Pacing-Induced Myocardial Ischemia"

Donald H. Penning, BSc, MD, Lawson Research Institute, St. Joseph's Health Centre, University of Western Ontario, London, Ontario, Canada:
"The Role of Glutamic Acid in Perinatal Hypoxic/Ischemic Encephalopathy"

Marc Sabbe, MD, University of California San Diego, La Jolla, CA:
"Studies on the Effects of Spinally Administered Drugs on Respiratory Function"

Beverly J.M. Waxler, MD, Cook County Hospital, Chicago, IL:
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BRAIN RESEARCH REVIEWS

A section of Brain Research devoted to the publication of review articles
Editor-in-Chief
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1300 Morris Park Avenue, Bronx, NY 10461, U.S.A.*

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Editorials

Intrathecal Morphine—An Underused Combination for Postoperative Pain Management

Robert K. Stoelting, MD

Discovery of opioid receptors in the substantia gelatinosa of the spinal cord has made possible new options for the effective management of postoperative pain (1). Specifically, neuraxial opioids administered by either the lumbar epidural or intrathecal route now make it feasible for anesthesiologists to offer selected patients a relatively pain free postoperative course. Although patient controlled analgesia and epidural injection of local anesthetics represent alternatives to neuraxial opioids, it is my bias that treatment with neuraxial opioids should be offered to the majority of patients undergoing operative procedures known to be associated with moderate to severe postoperative pain (i.e., thoracoabdominal operations, orthopedic procedures on major joints). If this treatment is accepted by the patient, it is my opinion that lumbar intrathecal administration of morphine is preferred to the epidural route for injection of morphine or any other opioid.

Intrathecal administration of opioids has the advantages of 1) simplicity; 2) reliability; 3) low dose requirements; and 4) absence of the need to place a catheter into the epidural space. Simplicity and reliability are assured by the technically easy identification of the subarachnoid space assuring proper placement of opioids. Dose-related side effects of opioids are minimized by achievement of analgesia with intrathecal doses of morphine that are 10 to 16 times less than doses required for epidural administration (2). Systemic effects from low doses of intrathecal opioids are unlikely, thus improving the predictability of the drug's pharmacologic effect. Potential risks of epidural catheter placement are avoided with intrathecal administration of opioids. In the absence of a catheter, however, intrathecal administration is limited to a single injection unless a repeat dural puncture is performed.

In contrast to identification of the subarachnoid space, confirmation of entrance into the epidural space may be equivocal. Equally important, epidural administration of opioids is complicated by pharmacokinetic aspects inherent in drugs placed in the epidural space. For example, the amount of drug that reaches receptors in the spinal cord by diffusion across the dura mater will be variably influenced by systemic absorption and sequestration into epidural fat. Indeed, systemic blood levels of morphine after epidural administration may be similar to those following intramuscular administration and precede achievement of therapeutic concentrations in the cerebrospinal fluid (1). To offset the effects of systemic absorption and fat sequestration, the epidural dose of opioids is about 10 to 16 times greater than that required for subarachnoid injection (2). Since undesirable side effects of neuraxial opioids are dose-related, there is undeniable logic in administering the lowest possible dose of opioid; this seems to only be predictably possible with intrathecal injection. The most important advantage of an epidural technique is the ability to repeat a dose of opioid using an epidural catheter. It must be remembered, however, that catheter insertion may not be a benign procedure, and there is no assurance that catheter migration will not occur between injections.

Several studies confirm that the quality and duration of analgesia after intrathecal injection of opioids equal or exceed those produced by epidural admin-

istration of morphine (2,4–7). In these same studies, evidence of depression of ventilation occurs after epidural morphine (5 mg) and not intrathecal morphine (250 μg) despite the fact that the mean duration of analgesia (28 hours for post cesarean section pain) produced by the lower dose of morphine exceeds that which follows epidural injection (2,4–7). Furthermore, use of minimal doses of intrathecal opioids does not prohibit the injection of small doses of systemic opioids such as fentanyl (12.5 to 25 μg administered intravenously) should analgesia be inadequate (4).

Pain relief following thoracotomy requires greater morphine doses than the 200 to 250 μg intrathecal injections found effective for pain relief following cesarean sections. It is likely that intrathecal morphine doses of 300 to 500 μg will provide adequate analgesia in the early postoperative period following this type of surgery. Nevertheless, increasing the intrathecal morphine dose to 10 μg kg^{-1} has not been demonstrated to increase the risk of depression of ventilation following thoracotomy (4).

Intrathecal injection of opioids is conveniently performed at the time local anesthetic is injected for a spinal anesthetic. Alternatively, the injection can be performed in the early postoperative period (4). A troublesome incidence of postspinal headache has not been observed in patients treated with intrathecal opioids. Perhaps this reflects use of 25-gauge needles in patients less than 50 years of age (4).

Just as I am convinced there are compelling reasons to select the intrathecal route over epidural administration, I am equally convinced that morphine is an appropriate selection for neuraxial injection. More lipid soluble opioids (i.e., fentanyl, sufentanil) produce intense but brief (often 6 hours or less) analgesia. This short duration of action relative to morphine would seem to limit use of these more lipid soluble opioids to catheter techniques which permit repeated injections (8–10). Epidural administration of sufentanil is associated with significant early depression of ventilation that most likely reflects combined systemic and neuraxial effects (8,9). Clearly, the most feared adverse side effect of morphine is delayed depression of ventilation presumably reflecting rostral spread of the opioid to vital medullary centers. The relatively poor lipid solubility of morphine (compared to sufentanil and fentanyl) is likely to result in more drug remaining in the cerebrospinal fluid for rostral spread (1). Indeed, delayed depression of ventilation has been observed following neuraxial injection of morphine but not fentanyl (1,10). Nevertheless, small doses of intrathecal morphine (200 to 500 μg) have not been associated with an unaccept-

able incidence of this life-threatening complication (4–6). Although close surveillance of adequacy of breathing (hourly nursing observation for sedation and ventilatory rate, perhaps monitoring with pulse oximetry) is mandatory there is increasing recognition that low dose neuraxial administration does not obligate patients to be observed in an intense monitoring environment (3,5). Awareness of reduced dosage needs in elderly patients or in those receiving systemic opioids is very important with respect to modifying doses of neuraxial opioids (11).

A possible and unique advantage of morphine is its propensity to diffuse from its lumbar site of injection to provide pain relief in areas innervated by thoracic portions of the spinal cord (1). It is not clear if more lipid soluble opioids that avidly attach to the spinal cord would diffuse sufficiently to produce the same distal effect on the spinal cord.

In the future, it is possible that nonopioids such as clonidine will find a role either alone or in combination with neuraxial opioids (12). Depression of ventilation is not a side effect of clonidine-induced analgesia while reduced doses of morphine made possible by the synergistic effects of a clonidine-morphine combination would also reduce the likely occurrence of opioid-induced depression of ventilation (13).

I believe the demonstrated advantages of intrathecal administration make this the preferable route of administration for neuraxial opioids. Adverse side effects, especially depression of ventilation, are an inherent risk of neuraxial opioids but the precise placement of small doses of opioids directly into the cerebrospinal fluid should minimize the incidence of this complication. My second conclusion is that morphine is the preferred opioid to inject into the intrathecal space. The duration of analgesia following intrathecal injection of morphine often exceeds 24 hours and additional analgesia, if still required, after this time is conveniently provided by patient controlled analgesia (5,6). In one report, analgesia provided by neuraxial opioids was judged superior to parenteral administration of opioids only in the first 24 hours postoperatively (14).

References

1. Cousins MJ, Mather LE. Intrathecal and epidural administration of opiates. Anesthesiology 1984;61:276–310.

2. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulfate for postcesarean analgesia—a clinical comparison. Anesthesiology 1988:925–9.

3. Ready LB, Oden R, Chadwick HS, Benedetti C, Rooke GA, Caplan R, Wild LM. Development of an anesthesiology-based postoperative pain management service. Anesthesiology 1988; 68:100–6.

4. Gray JR, Fromme GA, Nauss LA, Wang JK, Ilstrup DM. Intrathecal morphine for post-thoracotomy pain. Anesth Analg 1986;65:873–6.

5. Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for cesarean section. Anesth Analg 1988;370–4.

6. Abboud TK, Dror A, Mosaad P, Zhu J, Mantilla M, Swart F, Gangolly J, Silao P, Makar A, Moore J, David H, Lee J. Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg 1988;67:137–43.

7. Abboud TK, Moore M, Zuh J, Murakawa K, Minehart M, Longhitano L, Terrasi J, Klepper ID, Choi Y, Kimball S, Chu G. Epidural butorphanol or morphine for the relief of post-cesarean section pain: ventilatory responses to carbon dioxide. Anesth Analg 1987;66:887–93.

8. Van der Auwera D, Verborgh C, Camu F. Analgesic and cardiorespiratory effects of sufentanil and morphine in humans. Anesth Analg 1987;66:999–1003.

9. Whiting WC, Sandler AN, Lau LC, Chovaz PM, Slavchenko P, Daley D, Karen G. Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. Anesthesiology 1988;69:36–43.

10. Naulty J3, Datta S, Ostheimer GW, Johnson MD, Burger GA. Epidural fentanyl for post-cesarean delivery pain management. Anesthesiology 1985;63:694–8.

11. Ready L3, Chadwick HS, Ross B. Age predicts effective epidural morphine dose after abdominal hysterectomy. Anesth Analg 1987;66:1215–8.

12. Eisenach JC, Dewan DM, Rose JC, Angelo JM. Epidural clonidine produces antinociception, but not hypotension in sheep. Anesthesiology 1987;66:496–50.

13. Ossipov MH, Suarez LJ, Spaulding TC. Antinociceptive interactions between alpha-2 adrenergic and opiate agonists at the spinal level in rodents. Anesth Analg 1989;68:194–200.

14. Jayr, Mollie A, Bourgain JL, Alarcon J, Masselot J, Lasser P, Denjean A, Truffa-Bachi J, Henry-Amar M. Postoperative pulmonary complications: general anesthesia with postoperative parenteral morphine compared with epidural analgesia. Surgery 1988;104:57–63.

Epidural Opioids—The Preferred Route of Administration

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The Eighties have been marked by tremendous advances in our understanding of the etiology, mechanisms, and treatment of acute postoperative pain. Undeniably, the clinical application of neuraxial opioids to our analgesia armamentarium has been one of the most rewarding yet evocative issues to be debated by anesthesiologists in recent times. In the nine years since Wang published his experiences using intrathecal morphine for the control of chronic pain (1); the literature has been replete with studies aimed at identifying the most efficacious yet safe method of neuraxial opioid administration. One of the most important discoveries was that intrathecal morphine can cause delayed respiratory depression (2,3). Accordingly, attention shifted to the epidural administration of opioids as a means to lessen the risk of this dangerous side-effect. The result was that most clinical research performed on neuraxial opioids became focused on epidural administration by a variety of techniques. As experience with the epidural method of delivery accumulated, it became evident that the pain relief afforded by administration of opioids by this route is somewhat unpredictable. This is because central diffusion of opioids toward the spinal cord antinociceptive receptors is hampered by both systemic absorption and sequestration in epidural fat.

To avoid the vagaries of epidural administration, a growing number of anesthesiologists are beginning to advocate the use of intrathecal morphine. Indeed, there are those who suggest that perhaps intrathecal opioids should be considered the only rational method of postoperative pain relief (4). I disagree heartily with this view. While the argument in favor of greater utilization of intrathecal administration is to some extent logical, serious consideration must be given to the possibility of greater attendant morbidity. Virtually all studies comparing the incidence of side-effects of epidural to those of intrathecal opioids have shown the risks to be greater with the intrathecal route (5,6). At the same time, it has been demonstrated that intrathecal doses of morphine necessary for pain relief are significantly lower than those initially recommended (7,8). As these data are confirmed and refined, perhaps in the future such relative risks can be contained to a minimum.

The greatest advantage of using epidural narcotics is that they can be given through a catheter. This permits individualization of dosage by slow titration of opioid to optimum effect, and beyond that either repetitive intermittent dosing or continuous infusion of the drug allows prolongation of analgesia for many hours, if not days. Further, recent studies indicate that the epidural infusion of a combination of low-dose local anesthetic with an opioid may offer the best therapeutic effect while minimizing the risks of unwanted side-effects seen when higher doses of each of these drugs is given alone. Already the combination has been shown to be highly effective and safe in certain clinical settings and for certain patient categories, notably in upper abdominal, extensive intra-abdominal, and thoracic surgical patients (9,10). As a bonus, the administration of a local anesthetic-morphine combination will obtund the adverse neuroendocrine and stress responses associated with surgery (11). Epidural opioids alone are relatively ineffective in blunting these neurohumoral responses.

A means to unite the benefits of improved efficacy of intrathecally placed opioids with the flexibility of an in-dwelling epidural catheter may soon be realized. A dual lumen 18 and 22G epidural-spinal needle (E-SP® Neurodelivery Technology Inc., Tempe, Arizona) allows passage of a 29G spinal needle and administration of an intrathecal loading dose of morphine at the same time that an epidural catheter is placed. With the loading dose of morphine readily available for interaction with receptors in the substantia gelatinosa of the spinal cord, a continuous low-dose epidural infusion of morphine may then be initiated and fine tuned to maintain therapeutic neuraxial levels of morphine. One might anticipate that use of a very fine gauge needle to perforate the dura, together with the tamponade-effect of a subsequent epidural infusion would result in the risk of a post-dural puncture headache being exceedingly low.

While we continue to refine the details of intraspinal opioid administration for management of postoperative pain, there remains the pressing question of risk/benefit ratio. Is the cost of more intensive patient surveillance, necessary following intraspinal opioid administration, negated by shorter duration of hospitalization resulting from an accelerated recovery course? Should neuraxial opioid use be confined to patients undergoing extensive surgical procedures or at least to those at low risk of developing respiratory depression? With interest in acute pain management by anesthesiologists growing daily, these questions undoubtedly will be addressed and, hopefully, in the near future we may anticipate evolution of pain management protocols which not only provide the best risk/benefit ratio for the patient but also are readily accepted by patients and surgical and nursing staff. The now widespread clinical success of patient-controlled parenteral analgesia devices has underscored patients' preference for self-participation, or at least some autonomy from exclusive "physician control," in their choice for postoperative pain relief. At this juncture, then, it seems prudent to use the entire armamentarium of postoperative pain relief modalities available to us and provide individualized therapy rather than harness ourselves with a purportedly "best" technique applicable in all situations.

References

1. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979;50:149–50.

2. Liolios A, Andersen FH. Selective spinal analgesia. Lancet 1979;2:357.

3. Glynn CJ, Mather LE, Cousins MJ, Wilson PR, Graham JR. Spinal narcotics and respiratory depression. Lancet 1979;2:356–7.

4. Stoelting RK. Intrathecal morphine—an underutilized combination for postoperative pain management. Anesth Analg 1989;68:707–9.

5. Rawal N, Arner S, Gustafsson, Allvin R. Present state of extradural and intrathecal opioid analgesia in Sweden. Br J Anaesth 1987;59:791.

6. Cousins MJ, Mather LE. Epidural and intrathecal administration of opioids. Anesthesiology 1984;61:276–310.

7. Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for cesarean section. Anesth Analg 1988;67:370–4.

8. Abboud TK, Dror A, Mosaad P, Zhu T, Mantilla M, Swart F, Gangolly J, Silas P, Makar A, Moore J, David H, Lee J. Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg 1988;67:137–43.

9. El-Baz NM, Faber LP, Jensik RJ. Continuous epidural infusion of morphine for the treatment of pain after thoracic surgery: a new technique. Anesth Analg 1984;63:757–61.

10. Hjorts NC, Neumann P, Frsig F, Andersen T, Lindhard A, Rogon E, Kehlet H. A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. Acta Anaesthesiol Scand 1985;29:790–6.

11. Jorgensen BC, Andersen HB, Engquist A. Influence of epidural morphine on post operative pain, endocrine-metabolic, and renal responses to surgery. A controlled study. Acta Anaesthesiol Scand 1982;26:63–7.

Cerebral Blood Flow and Metabolism in Patients Undergoing Anesthesia for Carotid Endarterectomy

A Comparison of Isoflurane, Halothane, and Fentanyl

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The effects of isoflurane, halothane, and fentanyl on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) during anesthesia prior to carotid endarterectomy were compared using the intravenous method of 133-Xenon CBF determination. Patients, mean (±SE) age 68 ± 2, received either isoflurane (N = 16), 0.75% in O_2 and N_2O, 50:50; halothane (N = 11), 0.5% in O_2 and N_2O, 50:50; or fentanyl (N = 10), 5–6 μg/kg bolus and then 1–2 $μg \cdot kg^{-1} \cdot h^{-1}$ infusion in addition to O_2 and N_2O, 40:60. Measurements were made immediately before carotid occlusion. Mean (±SE) CBF $(ml \cdot 100\ g^{-1} \cdot min^{-1})$ was 23.9 ± 2.1 for isoflurane, 33.8 ± 4.8 for halothane, and 19.3 ± 2.4 for fentanyl. $CMRO_2$ $(ml \cdot 100\ g^{-1} \cdot min^{-1})$ was available from 22 patients and was 1.51 ± 0.28 for isoflurane (N = 7), 1.45 ± 0.24 for halothane (N = 6), and 1.49 ± 0.21 for fentanyl (N = 9). Although CBF was greater during halothane than during isoflurane or fentanyl anesthesia (p < 0.05), there were no demonstrable differences in $CMRO_2$ among the 3 agents. We conclude that choice of anesthetic agent for cerebrovascular surgery with comparable anesthetic regimens should not be made on the basis of "metabolic suppression." During relatively light levels of anesthesia, vasoactive properties of anesthetics are more important than cerebral metabolic depression with respect to effects on the cerebral circulation.

Key Words: BRAIN, BLOOD FLOW—metabolism.
ANESTHETICS, VOLATILE—halothane, isoflurane.
ANALGESICS, FENTANYL.

Two recent studies have suggested that the choice of anesthetic agent for carotid endarterectomy influences the incidence of ischemic EEG changes and the degree of reduction in cerebral perfusion necessary to cause such ischemic EEG changes (1,2). The lower blood flow threshold for EEG signs of ischemia observed with the use of isoflurane may represent a relative cerebral protective effect. However, the mechanism of such a proposed change in threshold is unclear at present; differences observed among anesthetic agents may be attributable to differing effects on cerebral blood flow (CBF) or different degrees of metabolic suppression. The present study was undertaken to compare prospectively the effects of three anesthetics regimens, including nitrous oxide and either isoflurane, halothane or fentanyl, on CBF and cerebral metabolic rate for oxygen ($CMRO_2$).

Methods

This protocol was approved by the Institutional Review Board of Columbia University College of Physicians and Surgeons and informed consent was obtained from patients scheduled to undergo elective carotid endarterectomy. All patients had symptoms referable to transient ischemic attacks. Premedication consisted of atropine (0.4 mg/70 kg i.m.) and oral

diazepam (10 mg/70 kg). All patients received 1–2 mg of midazolam i.v. during placement of catheters and monitoring devices. Monitoring included the use of a radial arterial catheter for arterial blood pressure transduction, temperature probe, capnography, and standard arterial blood gas analysis. Anesthesia was induced with thiopental, 4 mg/kg, and tracheal intubation facilitated by vecuronium 0.1 mg/kg. Patients were randomly assigned into one of three groups. Group 1 received isoflurane 0.75% in oxygen and nitrous oxide 50:50. Group 2 received halothane 0.5% in oxygen and nitrous oxide 50:50. Group 3 received 2.5 mg of droperidol and a bolus of 5–6 μg/kg of fentanyl followed by a continuous infusion of 1–2 μg·kg^{-1}·h^{-1} in addition to oxygen and nitrous oxide 40:60. Placement of CBF detectors was done after induction. Blood pressure was maintained at or slightly above the preoperative level by infusion of phenylephrine. Ventilation was controlled to maintain PaCO$_2$ at approximately 35 mm Hg.

After neck dissection and exposure of the jugular vein, a catheter was advanced approximately 5 cm from the angle of the mandible in a cephalad direction under direct vision by the neurosurgeon. This maneuver places the catheter tip in the region of the ipsilateral jugular bulb. CBF was measured after dissection and exposure of the carotid artery. Anesthetic depth remained constant during the period when the CBF measurement was taken; at least one hour elapsed from the time of induction of anesthesia. Measurement of CBF began before completion of jugular catheter placement in several cases, causing a 5–10 min temporal difference between the injection of the CBF tracer and jugular venous sampling. Surgical and anesthetic conditions remained constant during this period. Jugular venous and systemic arterial blood were sampled simultaneously for determination of cerebral arteriovenous oxygen content difference.

The CBF device, the Novo Cerebrograph 10a^R (Novo Diagnostic Systems, Bagsvaerd, Denmark) is a self-contained data collection system with 10 Na-I detectors encased in cylindrical lead collimators (3). The middle cerebral artery territory over each hemisphere was covered by 5 detectors. The channel analyzer window width was set to include the 81-KeV photo peak of 133-Xenon. Approximately 20 mCi of 133-Xenon in sterile saline was injected intravenously for each CBF measurement, resulting in peak count rates between 1000 and 3000 counts per 5-sec interval. A small plastic catheter was present in the endotracheal tube for sampling of end-tidal gas to determine tracer activity. The resultant air activity curve was used in deconvolution of the head curves and to

correct for recirculation of tracer. Clearance was recorded for 11 minutes. For environmental protection, exhaled gas from the patient was routed through an isolation valve into a xenon trap. Data were transferred to a PDP 11/73 computer for visual inspection of the individual detector head curves and their corresponding curve fits. Schroeder et al. have described the technical reliability of this methodology and equipment (3).

The CBF data are expressed as the Initial Slope Index (ISI) (4,5). This index reflects flow in both fast and slow compartments of the brain, but is weighted towards the fast compartment. It is inherently more stable than simple gray matter flow (Fg) during low-flow conditions. The ISI is derived from a monoexponential fitting performed on a theoretical curve constructed for a biexponential solution for the experimental data (5–7). In our experience, the ISI reliably describes hemodynamic changes in both awake (8) and anesthetized patients (9,10). The different models used for CBF calculation have been compared and discussed in detail elsewhere (11).

The pO$_2$ was determined using a standard blood gas analyzer (Instrumentation Laboratory 1303), with the oxygen content calculated as: {1.34} {Hb} {%Saturation} + {0.003} {pO$_2$}. Oxygen saturation was derived from the nomograms described by Kelman and Nunn (12). The product of arteriovenous differences of oxygen content and global mean of the 10 CBF detectors was used to calculate CMRO$_2$ as described previously (13).

Patients were categorized into four pre-operative risk groups using the grading system described by Sundt et al. (14) based upon angiographic findings, neurological status, and general health. Grade 1 includes patients under age 70 without significant medical or neurological risks. Grade 2 includes patients with angiographic risk factors such as contralateral carotid occlusion, long plaque or co-existing siphon stenosis. Grade 3 includes patients with symptomatic medical disease, such coronary artery or chronic obstructive pulmonary disease. Grade 4 includes patients that are neurologically unstable, with or without angiographic and medical risk factors.

To maximize statistical reliability and power in the testing of the overall effects of anesthetics, the mean of the 10 CBF detectors covering both MCA supply territories was taken as an index of global CBF (11,15–18). Although there may be some regional differences in perfusion due to underlying occlusive vascular disease (19), such variability would be expected to be primarily distributed along the major vascular supply territories. Further, although small infarcts and local occlusive disease may interact with the effects of

Table 1. Physiological Parameters

	Halothane (N = 11)	Isoflurane (N = 16)	Fentanyl (N = 10)
Mean arterial pressure (mm Hg)	96 ± 3	96 ± 3	98 ± 6
Heart rate (bpm)	65 ± 4	70 ± 3	56 ± 3*
PaCO$_2$ (mm Hg)	31.8 ± 1.1	32.6 ± 1.2	31.4 ± 0.8
Hemoglobin (g/dl)	12.2 ± 0.6	13.4 ± 0.6	12.9 ± 0.7
Temperature (°C)	35.5 ± 0.3	35.3 ± 0.2	35.7 ± 0.27

*Significantly different from isoflurane, $P < 0.05$.

anesthetic agents, such interactions were not the focus of this investigation. Data were analyzed using analysis of variance (ANOVA). If there were significant differences, post hoc testing was done using the Fisher Protected Least Significant Differences test. Non-parametric data were compared using contingency analysis. The threshold for significance was taken as $P < 0.05$. All results are expressed as mean ± SE.

Results

The sample consisted of 35 patients, mean age 68 ± 2 yrs and mean weight 73 ± 3 kg. There were 2 additional patients enrolled in the study but excluded because of an electrical malfunction in the rCBF data transfer routine, which was corrected for subsequent cases. In 10 cases jugular catheters were not placed. Jugular blood was not obtained in 5 cases because of technical malfunction in the jugular catheters or anatomical considerations. There was no difference among anesthetic groups with respect to weight or age. There were 18 females and 17 males, who underwent 37 operations (22 right-, 15 left-sided operations); 2 patients were operated on twice and received different anesthetics during each operation. Fifty-four percent were treated hypertensives, 19% were diabetic, and 38% carried the diagnosis of coronary artery disease. Sixteen cases were anesthetized with isoflurane, 11 with halothane, and 10 with fentanyl. Classification of cases into the risk groups (14) was as follows: 21 were evaluated as grade 1 or grade 2 and considered as low risk, and 16 were evaluated as grade 3 or 4 and considered high risk. By contingency analysis there was no significant difference with respect to the distribution of risk groups to different anesthetic groups.

There were no differences in other physiological variables (Table 1) among anesthetic groups, except for heart rate (bpm) which was significantly higher with isoflurane (70 ± 3) than with fentanyl (56 ± 3). For the entire sample (N = 37), global mean CBF was
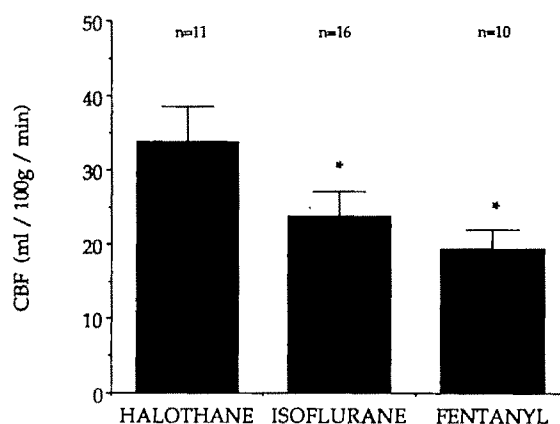
Figure 1. Mean (±SE) cerebral blood flow (CBF) immediately prior to carotid occlusion. *Significantly different from halothane, $P < 0.05$.
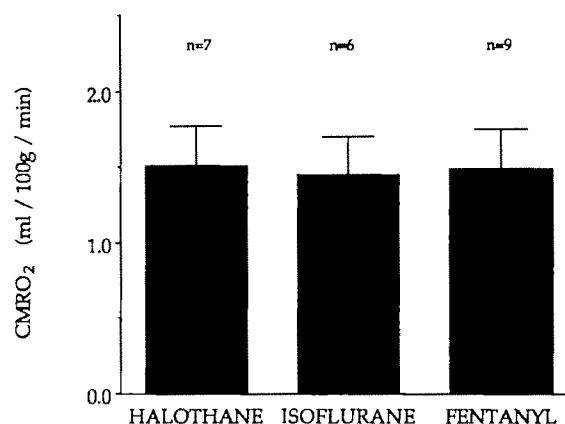
Figure 2. Mean (±SE) cerebral metabolic rate for oxygen immediately prior to carotid occlusion (CMRO$_2$). No statistically significant differences between groups.

24.7 ± 2 ml·100 g^{-1}·min^{-1}. As shown in Fig. 1, CBF during halothane anesthesia was significantly greater than during fentanyl or isoflurane anesthesia. In the subset of patients who had jugular catheters placed (N = 22), the mean CMRO$_2$ for all groups was 1.51 ± 0.28 ml·100 g^{-1}·min^{-1} (Fig. 2). The mean CMRO$_2$ and variance for the 3 different groups were almost identical. In this subset, there was no statistically significant difference in CBF among the 3 anesthetic regimens, although the means were similar to the larger group of 37 cases.

Risk grouping did not significantly influence flow or metabolism, although high-risk patients (grades 3 and 4) consistently had slightly lower CBF and CMRO$_2$ values than low-risk (grades 1 and 2) patients. Those with hypertension and diabetes mellitus did not differ from disease-free patients with respect to cerebral perfusion and other physiological variables. Seventeen patients who received phenylephrine

during CBF determination (up to 40 μg/min) did not differ in CBF compared to those who did not when examined by ANOVA or simple linear regression of drug infusion rate against CBF. There was no difference among anesthetic groups with respect to the amount of phenylephrine administered.

Discussion

In this study, we attempted to use equipotent doses of halothane, isoflurane and fentanyl in combination with N₂O. For the inhaled agents, the dosage was approximately 1.4 MAC correcting for the influence of age and considering the additive effect of temperature (20). It is recognized that there are difficulties in comparing intravenous agent dosages to those of inhaled agents. In clinical terms, the 3 regimens chosen afforded a smooth induction, similar degrees of autonomic stability and rapid emergence.

The results of the present prospective study confirm that halothane is a more potent vasodilator than either isoflurane or fentanyl in elderly patients with cerebrovascular disease undergoing carotid endarterectomy in the period immediately before carotid occlusion. This observation is in agreement with other reports in this patient population (2) and other animal and human studies. However, we were unable to demonstrate a difference in CMRO₂ among the three groups of anesthetic agents. Isoflurane is clearly a potent metabolic suppressant in both animals and in humans (21,22). However, its cerebral metabolic effects under relatively light levels of anesthesia in an elderly population with cerebrovascular disease, in comparison to narcotic and halothane anesthesia, have not been previously reported. It is likely that the light level of anesthesia used accounts for this metabolic equivalence. Animal studies partly support this notion of metabolic equivalence of different agents in low doses (23). In man, Madsen and Cold (24) examined CBF and CMRO₂ using 133-Xe desaturation and AVDO₂ in patients undergoing craniotomy for supratentorial tumor. They compared 0.6 or 1.2 MAC isoflurane and halothane in 67% N₂O in oxygen. There was no difference in CMRO₂ between agents at either MAC equivalent concentration. The relative differences in CBF reported here between isoflurane, halothane, and fentanyl are similar to other reports in humans (2,25,26).

Since the means of the CMRO₂ values are so close, a much larger sample size would be necessary to demonstrate a statistically significant difference among agents. The similarity of the means suggest that even if CMRO₂ could be demonstrated to differ

among agents, it is unlikely that the small difference would be of clinical relevance. Awake CMRO₂ is approximately 3–3.5 ml·100 g^{-1}·min^{-1} in humans (27) and is reduced in elderly patients with cerebrovascular disease by roughly 30% (28). Despite mathematical correction for the contribution of the extracerebral compartments (6), the intravenous method of CBF determination and weighted mean blood flow values such as the ISI slightly underestimate true brain flow (29). This explains, in part, why CMRO₂ in this study appears to be low with regard to the expected reduction in CMRO₂ with this level of anesthesia, as compared to animal studies (21). The slight reduction in body temperature observed in this study also contributes to the relatively low CMRO₂. The jugular blood sampled for determination of arteriovenous oxygen content difference represents venous drainage from a somewhat different mixture of cortical and deep brain structures than that seen by the cortical CBF detector array. However, the mean values obtained from the hemispheric CBF detectors can be considered to be a reasonable approximation of true global blood flow (13,21). It is an well-accepted convention to use hemispheric or global mean CBF from multiple detector systems to describe hemodynamic effects of both cerebrovascular disease in general and the effects of various types of surgical revascularization (15,30,31). However, both the CBF and CMRO₂ must be interpreted cautiously because there may be either focal or regional areas in some patients that might cause under- or over-estimation of the true AVDO₂ or global CBF. Despite this caveat, all groups appeared to be similar clinically with respect to their risk grouping and other physiological variables and the relative differences between groups using the methodology employed should be valid. Use of arteriovenous oxygen differences to estimate CMRO₂ have been useful in other studies to examine the cerebral metabolic responses to general anesthetics (24,32), head injury (13), and hypothermic cardiopulmonary bypass (33–35).

The quest for true pharmacological protection of the brain has remained elusive at best and it remains unclear what the basic mechanism of the ideal "protective" agent should be. There are two general theoretical approaches to explain salutary effects observed with putative cerebral protective agents. For the purposes of discussion, we will refer to these two paradigms as "supply/demand" and "cellular" mechanisms. Cellular mechanisms would include specific actions such as calcium entry blockade, free radical scavenging, or excitatory amino acids antagonists. Supply/demand protective agents would favorably affect the gross coupling between supply and de-

mand in one of two ways (36). The first would be suppression of $CMRO_2$. Metabolic suppression of all cellular processes is almost certainly the mechanism of action for profound hypothermia. Cerebral protective properties have been ascribed to isoflurane and barbiturates by their ability to decrease $CMRO_2$ by depression of synaptic transmission; these anesthetics have no metabolic effect on non-functioning brain, i.e., one that has an isoelectric EEG. The second mechanism of action of a supply/demand protective agent would be to induce a favorable redistribution of cerebral blow towards an ischemic focus.

It has been suggested that isoflurane is a better choice than halothane in patients undergoing carotid endarterectomy on the basis of a difference in the critical CBF for occurrence of ischemic EEG changes (2). This conclusion, reached from retrospective human studies, has been recently challenged in a preliminary report of ischemic thresholds in a rat model of forebrain ischemia (37). Regardless of an electrophysiological "protective" effect in regional ischemia, there is no evidence that isoflurane is superior to other equipotent anesthesia regimens in the ability to improve functional outcome in humans or in animal models (2,38,39).

There is evidence that anesthetics that are cerebral vasodilators are not desirable in the setting of cerebral ischemia. The present study and others have demonstrated that isoflurane is a less potent cerebral vasodilator than halothane, at least in the cerebral cortex. In a normal brain, greater cerebral vasodilation with halothane, relative to isoflurane and fentanyl, could theoretically have the potential of diverting blood away from an ischemic focus under conditions of carotid occlusion or after an embolic event. This is the phenomenon of "cerebral steal" and an analogous situation has been described during carotid endarterectomy under relative hypercarbia (40). Assuming that the relative electrophysiological protection is due to "supply/demand" and not to cellular mechanisms, our data support the notion that relative changes in CBF are more important factors than pure metabolic suppression when comparing the effects of anesthetic agents on the cerebral circulation. An intriguing question that must await further study is whether anesthetic-induced cerebral vasodilation or direct acting vasodilation (i.e., with carbon dioxide) affect outcome from an ischemic insult in a similar manner.

Strictly on the basis of our results, we can not recommend the preferential use of one or the other of the anesthetic regimens used in the present study for anesthetic management during carotid endarterectomy. However, the notion that isoflurane is superior to other volatile agents or narcotic techniques simply on the basis of its effect on suppressing cerebral metabolism is not warranted, if used in the concentrations employed in this study in conjunction with N_2O. It is important to compare further the cerebral effects of narcotic and inhalation anesthetic techniques used clinically. If there are no differences in their relative effects on neurological outcome, either clinically or electrophysiologically, then anesthetic management can be made more rationally on the basis of other cardiovascular considerations. This is especially pertinent to the patient undergoing carotid endarterectomy because of a very high incidence of concomitant coronary arteriosclerotic disease. Further studies must define the impact of anesthetic agents on either ischemic flow thresholds and/or clinical outcome. If there is no substantive difference among clinically relevant anesthetic regimens with respect to metabolic suppression, and relative cerebral protective properties are strictly a function of their effect on cerebrovascular resistance, then perhaps a different approach to selection of anesthetic agent could be taken. Anesthetic agents could be chosen on the basis of other cardiovascular considerations, and cerebrovascular resistance could be manipulated by other means.

References

1. Messick JM, Casement B, Sharbrough FW, Milde LN, Michenfelder JD, Sundt TM. Correlation of regional cerebral blood flow (rCBF) with EEG changes during isoflurane anesthesia for carotid endarterectomy. Critical rCBF. Anesthesiology 1987;66: 344-9.

2. Michenfelder JD, Sundt TM, Fode N, Sharbrough FW. Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. Anesthesiology 1987;67:335-40.

3. Schroeder T, Holstein P, Lassen NA, Engell HC. Measurement of cerebral blood flow by intravenous 133-Xenon technique and a mobile system. Neurological Research 1986;8:237-42.

4. Risberg J, Ali Z, Wilson EM, Wills EL, Halsey JH Jr. Regional cerebral blood flow by 133-Xenon inhalation. Stroke 1975;6: 142-7.

5. Prohovnik I, Knudsen E, Risberg J. Theoretical evaluation and simulation test of the initial slope index for noninvasive rCBF. In: Hartmann A, Hoyer S, eds. Cerebral Blood Flow, and Metabolism Measurement. Berlin: Springer-Verlag, 1985:56-60.

6. Obrist WD, Thompson HK, Wang HP, et al. Regional cerebral blood flow estimated by 133-Xenon inhalation. Stroke 1975;6: 245-56.

7. Prohovnik I, Knudsen E, Risberg J. Accuracy of models and algorithms for determination of fast-compartment flow by non-invasive 133-Xenon clearance. In: Magstretti PL, ed. Functional Radionuclide Imaging of the Brain. New York: Raven Press, 1983:89-117.

8. Maximillian VA, Prohovnik I, Risberg J. Cerebral hemodynamic response to mental activation in normo- and hypercapnia. Stroke 1980;11:342-7.

9. Young WL, Solomon RA, Prohovnik I, Ornstein E, Weinstein J, Stein BM. 133-Xe blood flow monitoring during arteriovenous malformation resection: a case of intraoperative hyperperfusion with subsequent brain swelling. Neurosurgery 1988; 22:765-9.

10. Young WL, Prohovnik I, Ornstein E, Sisti MB, Solomon RA, Stein BM, Ostapkovich N. Monitoring of cerebral hemodynamics before and following arteriovenous malformation resection. Anesth Analg 1988;67:1011-4.

11. Young WL, Prohovnik I, Ornstein E, Lucas R, Wang TST, Correll JW, Alderson PO. Rapid intraoperative monitoring of cerebral blood flow using 133-Xenon. J Cereb Blood Flow Metab 1988;8:691-6.

12. Kelman GR, Nunn JF. Nomograms for correction of blood PO₂, PCO₂, pH and base excess for time and temperature. J Appl Physiol 1966;21:1484.

13. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients with acute head injury. J Neurosurg 1984;61:241-53.

14. Sundt TM, Sharbrough FW, Piepgras DG, et al. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy. Mayo Clin Proc 1981;56:533-43.

15. Symon L. The use of cerebral blood flow measurements in clinical neurosurgery. In: S. Knezevic, et al., eds. Handbook of rCBF. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988:197-218.

16. Bishop CCR, Butler L, Hunt T, Burnand KG, Browse NL. Effect of carotid endarterectomy on cerebral blood flow and its response to hypercapnia. Br J Surg 1987;74:994-6.

17. Schroeder T, Sillesen H, Sorensen O, Engell H. Cerebral hyperperfusion following carotid endarterectomy. J Neurosurg 1987;66:824-9.

18. Schroeder T, Sillesen H, Engell H. Hemodynamic effect of carotid endarterectomy. Stroke 1987;18:204-9.

19. Tatemichi TK, Prohovnik I, Mohr JP, Correll JW, Quest DO, Jarvis L. Reduced hypercapnic reactivity in moyamoya disease. Neurology 1988;38:1575-81.

20. Cullen DJ. Anesthetic Depth and MAC. In: Miller RD, ed. Anesthesia. 2nd ed. New York: Churchill Livingstone, 1986: 553-80.

21. Todd MM, Drummond JC. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 1984;60:276-82.

22. Madsen JB, Cold GE, Hansen ES, Bardrum B, Kruse-Larsen C. Cerebral blood flow and metabolism during isoflurane-induced hypotension in patients subjected to surgery for cerebral aneurysms. Br J Anaesth 1987;59:1204-7.

23. Stullken EH jr, Milde JH, Michenfelder JD, Tinker JH. The non-linear responses of cerebral metabolism to low concentration of halothane, enflurane, isoflurane and thiopental. Anesthesiology 1977;46:28-34.

24. Madsen JB, Cold GE. Cerebral blood flow and oxygen uptake during anesthesia with halothane, enflurane, or isoflurane: a comparative study of cerebral protection. J Cereb Blood Flow Metab 1987;7(suppl 1):S628.

25. McKay RD, Sundt TM, Michenfelder JD, et al. Internal carotid artery stump pressure and cerebral blood flow during carotid endarterectomy: modification by halothane, enflurane, and Innovar. Anesthesiology 1976;45:390-9.

26. Eintrei C, Lesziewski W, Carlsson C. Local application of 133-Xenon for measurement of regional cerebral blood flow (rCBF) during halothane, enflurane, and isoflurane anesthesia in humans. Anesthesiology 1985;63:391-4.

27. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959;39:183-238.

28. Powers WJ, Raichle ME. Positron emission tomography and its application to the study of cerebrovascular disease in man. Stroke 1985;16:361-76.

29. Obrist WD, Wilkinson WE. Stability and sensitivity of CBF indices in the non-invasive 133-Xenon method. In: Hartmann A, Hoyer S, eds. Cerebral Blood Flow, and Metabolism Measurement. Berlin: Springer-Verlag, 1985:30-6.

30. Maximillian VA, Brawanski A. Functional and vascular challenge procedures during noninvasive rCBF measurements. In: Knezevic et al., eds. Handbook of rCBF. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988:79-122.

31. Hartmann A. Measurement of cerebral blood flow in cerebrovascular diseases: Neurology Part I. In: S. Knezevic, et al., eds. Handbook of rCBF. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988:157-88.

32. Newman B, Gelb AW, Lam AM. The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. Anesthesiology 1986;64: 307-10.

33. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of PaCO₂. Anesth Analg 1987;66:825-32.

34. Woodcock TE, Murkin JM, Farrar JK, Tweed WA, Guiraudon GM, McKenzie FN. Pharmacologic EEG suppression during cardiopulmonary bypass: cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. Anesthesiology 1987;67:218-24.

35. Rogers AT, Prough DS, Angert KC, Stump DA, Butterworth JF, Phipps J. Hypercarbia depresses cerebral oxygen consumption during hypothermic cardiopulmonary bypass. Anesth Analg 1988;67:S187.

36. Messick JM, Newberg LA, Nugent WM, Faust RJ. Principles of neuroanesthesia for the non-neurosurgical patient with CNS pathology. Anes Analg 1985;64:143-74.

37. Zhou J, Todd MS, Warner DS. Cerebral ischemic thresholds during halothane/N₂O and isoflurane/N₂O anesthesia. Anesthesiology 1988;69:A580.

38. Nehls DG, Todd MM, Spetzler RF, Drummond JC, Thompson RA, Johnson PC. A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. Anesthesiology 1987;66:453-64.

39. Baughman VL, Hoffman WE, Miletich DJ, Albrecht RF, Thomas C. Neurologic outcome in rats following incomplete cerebral ischemia during halothane, isoflurane or N2O. Anesthesiology 1988;69:192-8.

40. Boysen G, Ladegaard-Pedersen JH, Henriksen H, Olesen J, Paulson OB, Engell HC. The effects of PaCO₂ on regional cerebral blood flow and internal carotid arterial pressure during carotid clamping. Anesthesiology 1971;35:286-300.

The Effect of Nitroglycerin on Response to Tracheal Intubation

Assessment by Radionuclide Angiography

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The effect of intravenous (IV) nitroglycerin (NTG) on perioperative myocardial ischemia as detected by single pass radionuclide angiocardiography was studied in 20 patients scheduled for elective coronary artery bypass grafting (CABG). Ten patients, selected at random, received IV NTG 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (NTG group) and 10 others, IV saline (control group). Anesthetic induction consisted of midazolam 0.2 $mg \cdot kg^{-1}$, vecuronium 0.1 $mg \cdot kg^{-1}$, and 50% N_2O in O_2. ECG leads I, II, and V5 were monitored for ST segment changes. Single pass radionuclide angiocardiography (RNA) was performed at 5 times: prior to induction, prior to tracheal intubation, and at 1, 3.5, and 6 min following intubation. The presence of new regional wall motion abnormalities (RWMA) was determined from each RNA study as compared with the preinduction measurement. Apart from one patient in the control group who developed a new "v" wave after intubation, there was no evidence of ischemia by pulmonary capillary wedge pressure. No ECG evidence of ischemia was detected in any patient. Despite this, new regional wall motion abnormalities were observed in 3 patients in the control group and 1 patient in the NTG group. Blood pressure and heart rate responses of patients with new RWMA were not significantly different from other patients. The low incidence of ischemia in this population precludes a definitive statement regarding the efficacy of IV NTG, but the lower incidence of RWMA in the NTG group suggests a protective effect.

Key Words: HEART, RADIONUCLIDE ANGIOGRAPHY. MEASUREMENT TECHNIQUES, RADIONUCLIDE ANGIOGRAPHY. INTUBATION, TRACHEAL. PHARMACOLOGY, NITROGLYCERIN.

Prevention of perioperative ischemia is a major goal in anesthetizing patients with coronary artery disease. The importance of this goal was recently reemphasized by data suggesting an association between perioperative ischemia and infarction (1). Efforts to avoid ischemia have consisted principally of maintaining a hemodynamic milieu compatible with a favorable oxygen supply/demand ratio (i.e. avoiding hypoxia, anemia, tachycardia, and extremes of blood pressure). However, the introduction of more sensitive monitors of myocardial function reveals that ischemia can occur despite a "normal" hemodynamic course and a normal ECG (2,3).

Intravenous nitroglycerin (NTG), well known for its beneficial effects in ischemic heart disease, has been utilized prophylactically for perioperative ischemia. When evaluated in patients with ischemic coronary artery disease at a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ it did not prevent ischemia. A subsequent study has shown that 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is an inadequate dose and that 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ will prevent ischemia (4,5).

Previous studies have utilized ECG monitoring as the detector of ischemia. It has been shown that changes in regional wall motion are more rapid (6) and sensitive (7) in detecting ischemia than the ECG. However, detection of changes in regional wall motion requires baseline studies. We chose to evaluate the effectiveness of NTG infusion using radionuclide

angiography due to the ease of acquiring baseline studies. The studies were centered around the time of intubation since ischemia is frequent at this time (8) and could be caused in some patients by a sympathetic mediated coronary artery constriction (9,10). It is known that nitroglycerin can alleviate stress-induced coronary artery constriction. Our hypothesis was that the stress of intubation would provide coronary constriction manifested by regional myocardial ischemia detected by segmental dysfunction.

Methods

Patient Population

Following institutional review board approval and written consent, 20 male patients undergoing elective coronary artery bypass grafting were enrolled in this study. All patients had significant coronary artery disease, as defined by obstruction of 75% or greater of one or more major coronary arteries. Patients with significant valvular disease, those requiring pulsatile assist devices, and those requiring intravenous organic nitrates prior to randomization were excluded from the study.

Study Design

All patients received their usual cardiac medications on the day of surgery with the exception of oral organic nitrates. Premedication was accomplished with oral diazepam 0.1 mg·kg^{-1}, morphine sulfate 0.1 mg·kg^{-1} IM, and scopolamine 0.2 mg IM. Under local anesthesia, radial artery and thermodilution pulmonary artery catheters were inserted for hemodynamic monitoring. Patients were then randomized to either the NTG group and received intravenous nitroglycerin 1 μg·kg^{-1}·min^{-1} or to the control group which received saline. Nitroglycerin and saline infusions were continued for a minimum of 10 min before baseline radionuclide and hemodynamic measurements were obtained. Additional intravenous fluids were given to maintain a pulmonary capillary wedge pressure of approximately 15 mm Hg. Radionuclide measurements and pulmonary capillary wedge pressures were obtained at the following times: 1) baseline, patients breathing 100% O_2 by mask, 2) 2 min after anesthetic induction, 3) 1 min after tracheal intubation, 4) 3.5 min after intubation, and 5) 6 min after intubation. Pulmonary and radial artery pressures and ST segments from ECG leads I, II, and V5 were monitored and recorded continuously on a Surgery 7000 monitor manufactured by Marquette

Electronics, Inc. Greater than 1 mm of ST segment depression was considered indicative of myocardial ischemia.

Induction of anesthesia was accomplished with midazolam 0.2 mg·kg^{-1}, vecuronium 0.1 mg·kg^{-1}, and 50% N_2O in oxygen. Arterial blood gas tensions were measured at the beginning and end of the study to ensure adequate oxygenation and normocarbia.

Radionuclide Angiography

Radionuclide data were acquired using the Scinticor portable multicrystal gamma camera (Baird Corporation, Bedford, MA). At each study time, the gamma camera was placed in the anterior projection approximately 1 cm above the patient's chest. A 10 micro curie bolus of technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) was injected through a catheter in the superior vena cava for each study. To minimize cardiac motion due to respiration and changes in ventricular filling, all studies were performed at end-expiration.

Left ventricular function information was derived using computer software initially developed at this institution and now incorporated in the Scinticor (11,12). End-diastole (ED) and end-systole (ES) were automatically defined by the maximum and minimum radioactive counts, respectively, within a preliminary left ventricular region of interest. Summation of end-diastolic images during visualization of the left heart side provided an image of the left ventricle at end-diastole. An outline of the left ventricle was then drawn at the 21% isocount contour. To evaluate regional wall motion, the anterior projection of the left ventricle was divided into anterolateral, inferoapical, and inferobasal regions. Wall motion was reviewed by two blinded, experienced observers. For each study, wall motion was assessed by viewing a cinematic display of decreasing left ventricular count within each region. Each region was then graded on the following 10-point scale: 1, normal; 2–4, mild, moderate, and severe asyneresis; 5–7, mild, moderate, and severe akinesis; and 8–10, mild, moderate, and severe dyskinesis. An increase of 2 or more points in a region in consecutive studies was considered diagnostic of a new, significant wall motion abnormality. Additional hemodynamic variables recorded included HR, MAP, and PCWP.

Demographic data were compared with an unpaired t-test. Hemodynamic data were analyzed using repeated measures techniques. The association of RWMA with group was tested using a two-way contingency table and Fisher's exact test. Data are presented as means ± standard deviation.

Table 1. Demographics

	Control	NTG	
Age	54	60	P < 0.05
Coronary artery disease			
1 Vessel	2	1	NS
2 Vessel	1	3	NS
3 Vessel	7	6	NS
Ejection fraction at catheterization	51	50	NS
Medications			
Beta blockers only	2	1	NS
Calcium blockers only	1	2	NS
Beta and calcium blockers	6	7	NS
Angina class			
NYHA I	3	1	NS
NYHA II	2	2	NS
NYHA III	2	3	NS
NYHA IV	3	4	NS
Hypertension	5	4	NS
Myocardial infarction	5	4	NS

Control, Saline-treated group; NTG, Nitroglycerin-treated group; NS, $P > 0.05$; NYHA; New York Heart Association.

Results

A description of the study groups is presented in Table 1. With the exception of age, no difference between the groups was found. The mean ejection fraction was normal in both groups.

Hemodynamic variables are presented in Table 2. There was no difference between the two groups in heart rate, mean arterial pressure, or pulmonary capillary wedge pressure at any measurement point. Heart rate (HR) was unchanged in either group after induction with midazolam (Table 2). Heart rate increased after intubation compared with baseline in both groups: from 57 ± 16.9 to 69 ± 12.1 ($P < 0.05$) in the control group; from 58 ± 10.4 to 75 ± 15.3 ($P < 0.01$) in the NTG group. MAP increased above baseline in both groups after intubation. In the control group MAP was 89 ± 18.7 mm Hg at baseline versus 101 ± 20.9 after intubation ($P < 0.01$). The NTG group had a baseline of 88 ± 9.7 mm Hg and 100 ± 17.9 after intubation (NS).

The conventional indicators of ischemia showed little evidence of ischemia. ST segment analysis gave no indication of ischemia in either group at any study point. A new "v" wave (i.e. "v" wave >20 mm Hg) was observed in one patient in the control group after intubation. Otherwise, no elevation of pulmonary capillary wedge pressure suggestive of ischemia occurred in any patient.

Despite the lack of conventional indications of ischemia, new RWMA were noted in four patients after intubation: three patients in the control group, and only one in the NTG group. This difference did not reach statistical significance. No new RWMA

were noted after induction or before intubation. Localization of the affected region and the anatomical location of abnormal angiographic findings are summarized in Table 3.

Discussion

Perioperative ischemia is a frequent event, occurring in up to 50% of patients with coronary artery disease (1,8). It has been suggested that perioperative ischemia predisposes to post-operative infarction in patients having coronary bypass surgery (1). Although ischemia in the prebypass period is not a prerequisite for postoperative infarction (4) in cardiac surgical patients, development of methods to reduce the incidence and severity of ischemia is probably warranted.

We chose to study patients at intubation since this is a stressful procedure which is typically performed in a patient that is lightly anesthetized. This can produce a massive release of catecholamines, placing the patient with coronary artery disease (CAD) at risk for ischemia. Up to 50% of patients with CAD demonstrate ischemia at intubation (8). The hemodynamic responses to intubation that predispose patients to ischemia include, amongst others, increases in heart rate, mean arterial pressure, and pulmonary capillary wedge pressure, and decreased ejection fraction (12). These responses are thought to be a result of sympathetic nervous system response to tracheal intubation.

Diseased epicardial arteries respond to sympathetic activation with vasoconstriction (13,14), and this vasoconstriction can be abolished by IV NTG (15). It has been shown in the setting of catecholamine release that ischemia can be reversed by NTG in doses too small to affect global hemodynamics (i.e. rate pressure product) but sufficient to reverse vasoconstriction (9). This is the basis for our evaluation of NTG in the prevention of ischemia during stress of intubation. The dose used in this study did not significantly alter hemodynamics, but presumably altered coronary constriction. We did not, however, directly examine coronary vascular resistance nor diameter of coronary vessels to document altered coronary vasoconstriction.

Whether nitroglycerin is effective as a prophylactic treatment for ischemia in patients with ischemic coronary artery disease is controversial (5,8,15,16). In their initial work, Coriat et al. studied patients with symptomatic coronary artery disease undergoing non-cardiac procedures. They reported that an average dose of 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of NTG was more

Table 2. Hemodynamic Data: Heart Rate, Mean Arterial Pressure, and Pulmonary Capillary Wedge Pressure

Group	Variable	Baseline	After induction	After intubation 1 min	After intubation 3.5 min	After intubation 6 min
Control	HR mean	57	59	69*	63	60
	STD	16.9	11.8	12.1	12.1	12.3
	Map mean	89	74*	101+	86	82
	STD	18.7	13.2	20.9	16.2	14.7
	PCWP mean	22	19	21	21	21
	STD	6.0	3.4	5.3	5.3	6.5
NTG	HR mean	58	60	75+	71*	63
	STD	10.4	11.1	15.3	16.7	13.2
	Map mean	88	71*	100	93	83
	STD	9.7	6.2	17.9	17.1	14.2
	PCWP mean	21	17	19	19	12
	STD	3.7	4.0	5.2	5.2	3.4

NTG, nitroglycerin group; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; STD, standard deviation; *, $P < 0.05$ different from baseline; +, $P < 0.01$, different from baseline. Intergroup comparisons demonstrated no significant differences

Table 3. Correlation of Site of New Regional Wall Motion Abnormality to Angiographic Location of Coronary Artery Disease

Group	Site of RWMA	Percent occlusion of coronary arteries by angiography L MAIN	LAD	L CIRC	RCA
NTG	Apical	75	0	75	0
Control	Inferior	0	75	100	100
	Anterior	0	>75	0	0
	Apical inferior	0	100	100	95

Control, saline-treated; NTG, nitroglycerin-treated group; RWMA, Regional wall motion abnormality; L MAIN, left main; LAD, left anterior descending; L CIRC, left circumflex; RCA, right coronary artery.

effective at preventing ischemia, determined by Holter monitoring, than an infusion of a placebo (17). Thomson and colleagues studied NTG at a dose of 0.5 μg·kg^{-1}·min^{-1} in a double-blinded, randomized fashion. They could demonstrate no salutary effect in patients undergoing coronary bypass grafting (8). Coriat, again studying patients having non-cardiac procedures, reported that a dose of 1.0 μg·kg^{-1}·min^{-1} of NTG was more effective than 0.5 μg·kg^{-1}·min^{-1} (5). The benefit of NTG during non-cardiac surgery was again demonstrated by Fusciardi et al. (15). In a subsequent communication, Coriat postulated that patients with poor left ventricular function would benefit most from NTG infusion (18) since NTG is most effective in this setting (3). It is interesting that the mean ejection fraction of all patients in Thomson's study was normal (8). All the patients in our study had a normal ejection fraction. Whether prophylactic NTG is more effective in patients with compromised left ventricular function requires investigation.

Ischemia can be detected in several ways. Pulmonary artery pressure monitoring may reveal an eleva-

tion in wedge pressure (AC wave >15 mm Hg) or the appearance of a new "v" wave >20 mm Hg which implies ischemia (19). On the ECG, horizontal or downsloping depression of the ST segments of 0.1 mV or more for 0.08 sec or longer is the classic sign of ischemia. A decrease in ejection fraction can precede angina or ST changes (20). However, changes in regional wall motion are considered more sensitive than all of the above methods (6,20,21). It has been known since 1935 that the heart's contractile function is exquisitely sensitive to the adequacy of its perfusion (22). Since then, much work has been performed to confirm the concept that monitoring cardiac function is among the most sensitive techniques for the early diagnosis of ischemia (23). These studies uniformly demonstrate that the development of new RWMA as a result of ischemia always occurs in advance of ECG changes, and that this difference in time of onset is most distinct in the more clinically prevalent cases of partial coronary flow reduction. Therefore, radionuclide angiography should have the advantage of this early ischemia detection capability. However, it is important to realize that factors other than ischemia may have an influence on the measurement of RWMA. Hemodynamic alterations will clearly play a role in affecting overall cardiac function. Increases in impedance to ejection may diminish global endocardial wall motion. Enhancement of the contractile state will have the opposite effect. Finally, motion of the heart as a whole (translation and rotation within the thorax) may play a minor role in these determinations, although in this qualitative analysis, this factor is generally accommodated by the experience of the observer. Nonetheless, an ischemic event should be evident despite moderate hemody-
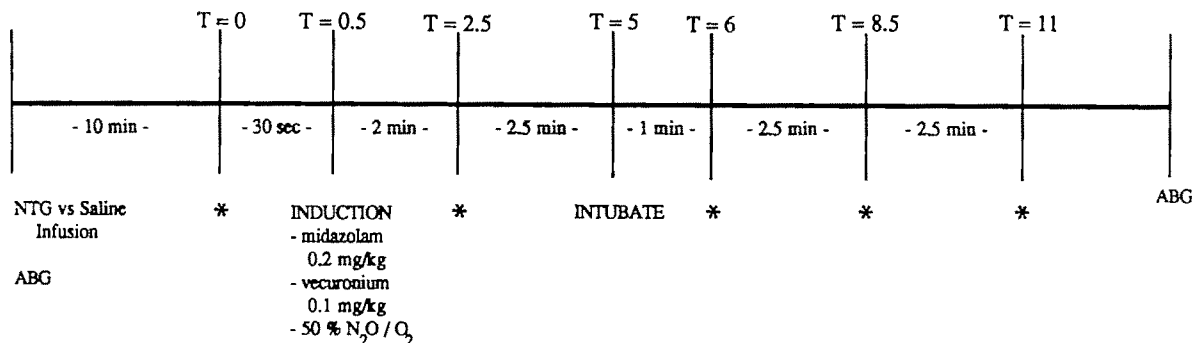
Figure 1. Nitroglycerin randomization during endotracheal intubation.

namic changes, since its effect will be within a specific region, while hemodynamic effects are of a global character. If new RWMA does reflect ischemia as many investigators believe, then a greater sensitivity of RWMA for detecting ischemia is demonstrated over conventional measures.

Radionuclide cardioangiography was utilized because it provides accurate measures of regional wall motion (11,12,24) combined with ease of acquiring baseline measurements. This method has not been used previously to investigate the protective effect of NTG during anesthesia. Two methods are typically employed: first pass and equilibrium measurements. First pass studies are obtained after an intravenous injection of the radiotracer. Since data are obtained within 30 sec, transient events may be detected. Equilibrium studies are performed after establishing a steady-state level of radiation in the circulatory volume (e.g. technetium labelled red blood cells). Images are recorded over a period of time and coordinated or "gated" with ECG (25). Both techniques can determine end-systolic and end-diastolic areas and measure ejection fraction and regional wall motion. First pass methods were utilized in this study to more rapidly evaluate ventricular responses to stress. Interestingly, the correlation between the location of RWMA and coronary angiography evidence of arterial disease seen in Table 3 is weak. This is probably due to the fact that during the determination of RWMA the heart was divided into three large areas that do not necessarily correlate with coronary anatomy.

Midazolam is a safe induction agent for patients with coronary artery disease (16); however, induction with benzodiazepines is associated with a transient sympathetic response (26). A midazolam induction causes small decreases in mean aortic pressure, LV

end-diastolic pressure, cardiac index, and stroke index. An increased heart rate (+8%) is typically noted with no change in systemic vascular resistance or maximum velocity of shortening. These changes are not associated with myocardial ischemia as judged by the absence of changes in the ECG, myocardial lactate extraction, and relaxation time constant (16). Changes noted in hemodynamics in this study after induction with midazolam were consistent with those expected with this technique (16). Mean arterial pressure and pulmonary capillary wedge pressure decreased slightly. However, there was no significant increase in heart rate. The induction of anesthesia was not associated with ECG evidence of ischemia in any patient. All changes in regional wall motion occurred after intubation. A moderate increase in MAP between baseline and the initial post-intubation measurements occurred in both the control and NTG groups. The effects of these changes on RWMA are not completely predictable since they could have resulted from increases in either systemic vascular resistance or contractility or both, which would tend to offset each other. Moreover, the fact that the wall motion abnormalities observed were discreet regional events make them more likely to have been of ischemic origin. Previous studies using fentanyl and pancuronium have found a 63% incidence of ischemia (5). The incidence of ischemia in this study was only 30%. Reasons for this low incidence of ischemia using midazolam and vecuronium compared with fentanyl and pancuronium deserve further investigation.

At no point in our study was there any indication of ischemia on the ECG. Despite this, four patients showed new regional wall motion abnormalities after induction. This is consistent with the hypothesis that RWMA are indicators of ischemia not detected by ECG, and that NTG provides protection. In the

control group three of ten developed RWMA, and in the NTG group, one of ten developed RWMA. This difference did not reach statistical significance, but the trend suggests a beneficial effect of nitroglycerin.

In conclusion, new wall motion abnormalities occur after tracheal intubation in the absence of ECG and hemodynamic markers of ischemia. Nitroglycerin tends to prevent the wall motion abnormalities providing presumptive evidence for a sympathetic mediated coronary artery constriction mechanism. Although these data are suggestive of a protective effect by NTG and demonstrate the sensitivity of wall motion abnormalities in detecting ischemia, additional observations with more direct quantitation of motion abnormalities might be necessary to fully support this view.

References

1. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.

2. Roizen MF, Beaupre PN, Alpert RA et al. Monitoring with two-dimensional transesophageal echocardiography. J Vasc Surg 1984;1:300–5.

3. Smith JS, Cahalan MK, Benefiel DK et al. Intraoperative detection of myocardial ischemia in high risk patients: electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 1985;65:1015–21.

4. Yousif H, Davies G, Westaby JS, Prendiville OF, Sapsford RN, Oakley CM. Preoperative myocardial ischaemia: its relation to perioperative infarction. Br Heart J 1987;58:9–14.

5. Coriat P, Daloz M, Bousseau D, Fusciardi J, Echter E, Viars P. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous nitroglycerin. Anesthesiology 1984;61:193–6.

6. Clements FM, de Bruijn NP. Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. Anesth Analg 1987;66:249–61.

7. Coriat P, Harari A, Daloz M, Viars P. Clinical predictors of intraoperative myocardial ischemia in patients with coronary artery disease undergoing noncardiac surgery. Acta Anaesthesiol Scand 1982;26:287–90.

8. Thomson IR, Mutch WA, Culligan JD. Failure of intravenous nitroglycerin to prevent intraoperative myocardial ischemia during fentanyl-pancuronium anesthesia. Anesthesiology 1984;61:385–93.

9. Brown BG, Lee AB, Bolson EL, Dodge HT. Reflex constriction of significant coronary stenosis as a mechanism contributing to ischemic left ventricular dysfunction during isometric exercise. Circulation 1984;70:18–24.

10. Feigl EO. The paradox of adrenergic coronary vasoconstriction. Circulation 1987;76:737–45.

11. Upton MT, Rerych SK, Newman GE, Bounous EP Jr, Jones RH. The reproducibility of radionuclide angiographic measurements of left ventricular function in normal subjects at rest and during exercise. Circulation 1980;62:126–32.

12. Giles RW, Berger HJ, Barash PG et al. Continuous monitoring of left ventricular performance with the computerized nuclear probe during laryngoscopy and intubation before coronary artery bypass surgery. Am J Cardiol 1982;50:735–41.

13. Brown BG. Response of normal and diseased epicardial coronary arteries to vasoactive drugs: quantitative arteriographic studies. Am J Cardiol 1985;56:E23–9.

14. Mudge GH, Grossman W, Mills RM, Lesch M, Braunwald E. Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N Engl J Med 1976;295:1333–7.

15. Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Krayenbuehl HP. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. Circulation 1986;73:865–76.

16. Marty J, Nitenberg A, Blanchet F, Zouioueche S, Desmonts J. Effects of midazolam on the coronary circulation in patients with coronary artery disease. Anesthesiology 1986;64:206–10.

17. Coriat P, Fusciardi J, Daloz M, Harari A, Ducardonet A, Viars P. Prevention de l'ischemie myocardique per-operatoire: Emploi d'une perfusion continue de trinitrial. Ann Fr Anesth Reanim 1982;1:47–51.

18. Coriat P. Intravenous nitroglycerin dosage to prevent intraoperative myocardial ischemia during noncardiac surgery. Anesthesiology 1986;64:409–10.

19. Kaplan JA, Wells PH. Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 1981;60:789–93.

20. Upton MT, Rerych SK, Newman GE, Port S, Cobb FR, Jones RH. Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. Circulation 1980;62:341–9.

21. Roizen MF, Beaupre PN, Alpert RA, Kremer P, Cahalan MK, Stoney RJ. Monitoring with two-dimensional transesophageal echocardiography. J Vasc Surg 1984;1:300–3.

22. Tennant R, Wiggers C. The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935;112:351–61.

23. Clements F, de Bruijn N. Perioperative evaluation of regional wall motion by transesophageal echocardiography. Anesth Analg 1987;66:249–61.

24. Jones RH, McEwan P, Newmann GE, et al. Accuracy of diagnosis of coronary artery disease by radionuclide measurement of left ventricular function during rest and exercise. Circulation 1981;64:586–601.

25. Commin P, Coriat P, Foauchet M, et al. Radionuclide assessment of cardiac function. Anaesthesia 1984;39:319–23.

26. Menkhaus PG, Reves JG, Kissin I, et al. Cardiovascular effects of esmolol in anesthetized humans. Anesth Analg 1985;64:327–34.

Comparison of Bupivacaine- and Ropivacaine-Induced Conduction Blockade in the Isolated Rabbit Vagus Nerve

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BADER AM, DATTA S, FLANAGAN H, COVINO BG. Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1989;68:724–7.

Ropivacaine (LEA-103) is a new amino-amide local anesthetic agent the chemical structure and anesthetic properties of which are similar to bupivacaine. Preliminary studies in animals indicate that the CNS toxicities of ropivacaine and bupivacaine are similar, but that ropivacaine may have less arrhythmogenic effects than bupivacaine. The current study was designed to compare the in vitro potency, onset and recovery from block of ropivacaine and bupivacaine using an isolated rabbit vagus nerve model. The effect of varying concentrations of ropivacaine and bupivacaine on the com-

pound action potential of A and C nerve fibers was assessed to determine whether motor and sensory fibers have different sensitivities to the two agents. The results showed that the depressant effect of bupivacaine was 16% greater than that of ropivacaine on motor fibers, but only 3% greater on sensory fibers. An analysis of variance indicated that this was a statistically significant difference (P = 0.028). Thus, at the concentrations tested, ropivacaine appears to produce relatively less blockade of motor fibers than does bupivacaine but with similar sensory blockade. The onset of this difference became significant as early as five minutes after the drug exposure was begun. No significant differences in recovery times were observed.

Key Words: ANESTHETICS, LOCAL—bupivacaine, ropivacaine.

The rapid intravascular injection of bupivacaine has been associated with the development of ventricular arrhythmias and sudden cardiovascular collapse (1–3). This has generated interest in the development of a local anesthetic agent with potency and duration similar to that of bupivacaine but with potentially less cardiotoxicity. Ropivacaine (LEA 103, S-(-)-1-Propyl-2',6'-pipecoloxylidide hydrochloride monohydrate, the propyl homologue of bupivacaine) is a new amide local anesthetic, the pKa and plasma protein binding properties of which are similar to those of bupivacaine, but which is less lipid soluble than bupivacaine (4). In addition, ropivacaine is prepared as the S isomer whereas bupivacaine is a racemic mixture. In dogs ropivacaine is slightly less potent than bupivacaine in terms of motor blockade following epidural and intrathecal administration (5). Similar potency in sensory anesthesia has been ob-

served following sciatic nerve block and epidural block in guinea pigs (6). The convulsant dose is almost identical to that of bupivacaine, indicating similar central nervous system toxicity (7). However, at equivalent doses and plasma concentrations, bupivacaine causes a greater number of ventricular arrhythmias and deaths than ropivacaine (7). In vitro, ropivacaine has cardiac electrophysiological effects that are less depressant and of shorter duration than those of bupivacaine (8). The current study was designed to compare the in vitro potency and the onset and recovery of block of ropivacaine to that of bupivacaine using an isolated rabbit vagus nerve model. The effect of varying concentrations of ropivacaine and bupivacaine on the compound action potential of A and C nerve fibers was also assessed to determine whether motor and sensory fibers would exhibit differential sensitivity to the two anesthetic agents.

Methods

Vagus nerves obtained from New Zealand white rabbits (4–5 kg) were used for this study. Animals

were housed in a National Institutes of Health approved animal care facility and were sacrificed in accordance with the guidelines for the care and use of laboratory animals. Animals were anesthetized with intravenous thiamylal (1.5 mg/kg) before being sacrificed by intravenous air embolus. Vagus nerves were rapidly removed with sheaths intact. Nerves were bathed in HEPES-Liley solution containing 136.8 mM NaCl, 5.0 mM KCl, 2.0 mM CaCl2, 1.0 mM MgCl2, and 11.0 mM dextrose buffered by the addition of 3.0 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES). The pH was adjusted to 7.35–7.40 by the addition of 0.1 N NaOH. The nerves were transferred to a stimulation chamber as previously described (9). The intact vagus nerves were stimulated using surface platinum electrodes with a Grass S46 stimulator and a Grass Stimulus Isolation Unit. The stimulation frequency was 0.5 Hz. Stimulus duration was 0.05 msec for A fibers and 1.0 msec for C fibers. Stimulus intensities were adjusted to obtain the maximum compound action potential (CAP) on a Tektroniks model 5113 storage oscilloscope. The experiments were performed at room temperature (22°C). Measurements of the compound action potential amplitude were made from photographs of the images displayed on the storage oscilloscope. The A and C fibers were identified by their respective conduction velocities of 25–50 m/sec and <1.0 m/sec. The nerves were bathed in HEPES-Liley solution until a steady-state baseline compound action potential was achieved. The nerves were then superfused with either bupivacaine or ropivacaine in concentrations of 0.1 mM, 0.15 mM, or 0.2 mM prepared in HEPES-Liley salt solution. Each drug concentration was tested on five or six animals. All solutions were administered at a rate of 14 to 16 drops per minute for 30 min. Compound action potential amplitudes of A and C fibers were recorded every 5 min during the time the nerve was bathed with the anesthetic agent. At the end of the 30 min exposure, the nerve was washed with HEPES-Liley solution until there was at least 80% to 90% recovery of control compound action potential in all fibers to ensure that the observed conduction blockade was not secondary to nerve damage. Results were expressed in terms of percent reduction in compound action potential amplitude at 5-min intervals during the 30-min exposure. The time for 80%–90% recovery of compound action potential was also recorded. The data were plotted in a linear fashion with the percent blockade (ordinate) against the anesthetic concentration expressed as the log concentration. Analysis of variance (ANOVA) and linear regression were used where
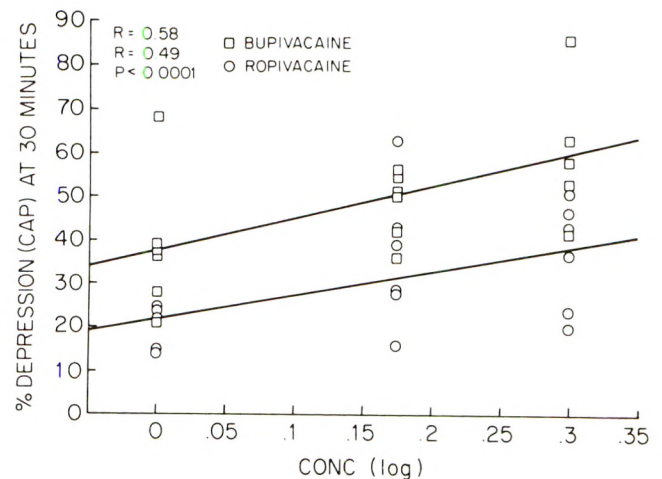
Figure 1. Dose-response curves comparing the percent depression of A fiber action potentials (AP) by ropivacaine (R = 0.49) and bupivacaine (R = 0.58) following 30 min of anesthetic exposure; a significant difference was present at all concentrations tested.
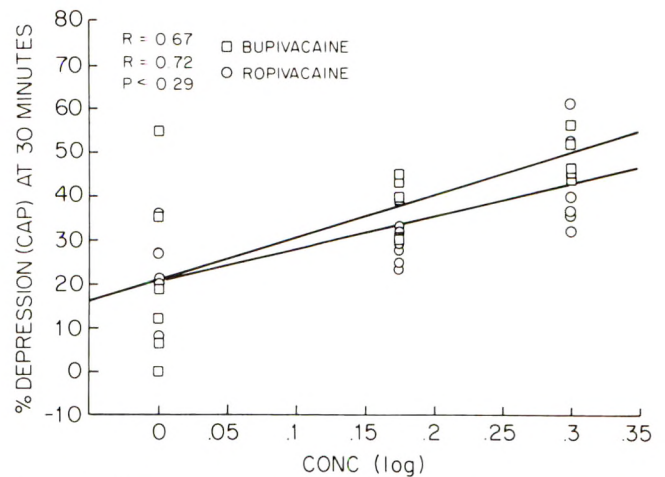
Figure 2. Dose-response curves comparing the percent depression of C fiber action potentials (AP) by ropivacaine (R = 0.72) and bupivacaine (R = 0.67) following 30 min of anesthetic exposure; no significant differences were present.

appropriate to compare groups. Statistical significance was assumed with P values less than 0.05.

Results

Figures 1 and 2 show the percent depression of the compound action potential of A and C nerve fibers versus the log concentration of anesthetic agent. The percent depression at the end of the 30-min anesthetic exposure increased in a concentration-dependent fashion with both ropivacaine and bupivacaine on both the A and the C fibers (Figures 1 and 2). The overall effects of bupivacaine across concentrations were 16% stronger than those of ropivacaine

Figure 3. Comparison of the percent depression of A fiber action potentials (AP) by ropivacaine and bupivacaine at 5-min intervals during a 30-min exposure; (*) indicates $P < 0.05$.

Figure 4. Comparison of the percent depression of C fiber action potentials (AP) by 0.2 mM ropivacaine and bupivacaine at 5-min intervals during a 30-min exposure; no significant differences were present.

Table 1. Time (min) to 80%–90% Recovery of Action Potential Amplitude (Mean ± sd)

Concentration	Bupivacaine	Ropivacaine	
0.1 mM	52 ± 12	40 ± 3.5	P < 0.06
0.15 mM	46 ± 21	51 ± 25	P < 0.81
0.2 mM	86 ± 23	63 ± 29	P < 0.25

tion period (Figure 3). The amount of C fiber depression seen with the two anesthetic agents was not significantly different throughout the period of drug exposure. At the lower concentration, the difference in A fiber depression seen with the two anesthetic agents was still present, but did not become statistically significant until after a 10–15 min exposure. No difference in the amount of C fiber depression was seen between the two agents.

The mean times for the nerve fiber action potentials to regain 80% to 90% of its initial pre-drug control value are shown in Table 1. There was no significant difference in recovery times of A and C fibers following exposure to ropivacaine and bupivacaine at any of the concentrations tested.

Discussion

In vivo studies in an experimental dog model have previously demonstrated that ropivacaine is less potent than bupivacaine in terms of producing motor blockade when used for epidural or spinal anesthesia (5). However, sciatic nerve block and epidural block data in guinea pigs indicated similarities in the onset, duration, and potency of sensory anesthesia produced by the two agents (5). The results of the present study utilizing an isolated rabbit vagus nerve model suggest that differences may exist between the two agents in the relative depression of sensory and motor fibers of the compound action potential. The effects of ropivacaine, relative to those of bupivacaine, are significantly less on A fibers than they are on C fibers. The depression of A fiber action potentials by ropivacaine was less than the depression produced by bupivacaine at the concentrations tested. No significant difference was demonstrated in the degree of depression of the action potential of C fibers produced by the two agents.

Comparison of the physico-chemical properties of ropivacaine and bupivacaine show that while the pKa values of the two agents are nearly identical (ropivacaine 8.0; bupivacaine 8.1), ropivacaine is less lipid soluble than bupivacaine in both sciatic nerve and subcutaneous fat (10). Therefore, there may be a difference in penetration of the larger myelinated A

on the A fibers, but only 3% stronger on the C fibers. An analysis of variance revealed that this difference represented a statistically significant anesthetic by fiber interaction (F = 5.07, P = 0.028). Post hoc tests showed that the effects of the two anesthetics differed significantly on the A fibers (P = 0.0001), but not on the C fibers (P = 0.29).

Figures 3 and 4 show the percent depression of the compound action potential of A and C nerve fibers as a function of time during exposure to a 0.2-mM concentration of either bupivacaine or ropivacaine. The degree of A fiber depression seen was significantly less in the ropivacaine-treated nerves as early as five minutes after the drug exposure began and continued to be less throughout most of the observa-

fibers by the two agents due to the high lipid content of myelin. The relatively greater lipid solubility of bupivacaine may allow this agent to penetrate the large, myelinated A fibers more rapidly than the less lipid soluble ropivacaine. With the unmyelinated, smaller C fibers, less difference was demonstrated between the two agents.

Rosenberg and Heinonen have previously studied the differential sensitivities of A and C fibers to bupivacaine and ropivacaine (11). Their study suggested that at higher concentrations, bupivacaine showed a tendency to cause a greater decrease in amplitude of the action potentials of the large A fibers than did ropivacaine. A statistical analysis was not included. Their study only compared mean effects after 4 and 8 minutes of anesthetic exposure, which may not have allowed enough time to elapse for the differential sensitivity of the two agents on A and C fibers to be clearly demonstrated.

The differential sensitivity of A and C fibers to ropivacaine has important clinical significance. For example, a local anesthetic that produces relatively greater sensory blockade and less motor blockade than bupivacaine would seem to be an ideal agent for use in labor. Clinical studies using ropivacaine for regional anesthesia in human subjects are currently underway. These studies will help to determine if the differential sensitivities seen in vitro in the present study are also present in the clinical setting.

References

1. Edde R, Deutsch S. Cardiac arrest after interscalene brachial plexus block. Anesth Analg 1977;56:446-447.

2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285-287.

3. Prentis J. Cardiac arrest following caudal anesthesia. Anesthesiology 1979;50:51-53.

4. Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amino-amide local anesthetic. Anesth Analg (In press)

5. Feldman HS, Covino BG. LEA-103 Comparative motor blocking effects of bupivacaine and ropivacaine, a new amino-amide local anesthetic, in the rat and dog. Anesth Analg (In press)

6. Akerman B, Sandberg R, Covino BG. Local anesthetic efficacy of LEA 103, an experimental xylidide agent. Anesthesiology 1986;65:A217.

7. Arthur GR, Feldman HS, Norway AAS, Doucette BA, Covino BG. Acute I.V. toxicity of LEA-103, a new local anesthetic, compared to lidocaine and bupivacaine in the awake dog. Anesthesiology 1986;65:A182.

8. Moller RA, Covino BG. Cardiac electrophysiologic effects of a new long acting local anesthetic agent (LEA-103). Anesthesiology 1986;65:A183.

9. Gissen AJ, Covino BG, Gregus J. Differential sensitivities of mammalian nerve fibers to local anesthetic agents. Anesthesiology 1983;53:467-474.

10. Rosenberg PH, Kytta J, Alila A. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into N-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. Br J Anaesth 1986;58:310-14.

11. Rosenberg PH, Heinonen E. Differential sensitivity of A and C nerve fibers to long-acting amide local anaesthetics. Br J Anaesth 1983;55:163-167.

Does Nitrous Oxide Affect the Hemodynamic Effects of Anesthesia Induction with Propofol?

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CARLIER S, VAN AKEN H, VANDERMEERSCH E, THORNILEY A, BYTTEBIER G. Does nitrous oxide affect the hemodynamic effects of anesthesia induction with propofol? Anesth Analg 1989;68:728–33.

Anesthesia was induced in 20 patients, ASA physical status I and II, with either propofol (2.5 $mg \cdot kg^{-1}$), vecuronium (100 $\mu g \cdot kg^{-1}$), and 100% oxygen (Group A), or with equal doses of propofol and vecuronium but with 70% nitrous oxide in oxygen (Group B). All patients were premedicated with lorazepam 2 mg orally. In both groups systolic arterial pressure decreased after 3 minutes ($P < 0.05$) due to decreases in cardiac output and stroke volume ($P < 0.05$). Systemic vascular resistance in both groups did not change immediately after administration of propofol but increased ($P < 0.05$) following intubation. Addition of nitrous oxide did not alter hemodynamic parameters associated with propofol induction.

Key Words: ANESTHETICS, INTRAVENOUS— propofol. ANESTHETICS, GASES—nitrous oxide.

Previous studies on the hemodynamic effects of anesthetic induction with propofol have reported conflicting data. Some authors found that the observed decreases in mean arterial pressure (MAP) were due to decreases in systemic vascular resistance (SVR) while cardiac output (CO) did not change (1). Others reported that marked decreases in CO and stroke volume (SV) were responsible for the decreases in MAP (2–4) and still others explained the decrease in MAP as a result of decreases in both CO and SVR (5–8). These differences in findings could, to some extent, be attributed to different protocols. In some studies patients were breathing spontaneously, in others they were artificially ventilated either with air, 100% oxygen, or 70% nitrous oxide in oxygen. Since N_2O has cardiovascular effects which are influenced by the interaction with other drugs (9–11) this study was performed to determine whether the hemodynamic effects of anesthetic induction with propofol are altered by simultaneous use of 70% of N_2O, which is still the most popular anesthetic adjuvant.

Material and Methods

Twenty patients (ASA physical status I and II) scheduled for elective major abdominal and thoracic surgery were studied. The study was approved by the hospital ethical committee and written informed consent was obtained from all patients. Patients did not qualify for this study if they were younger than 25 or older than 60 years, were obese (>120% of ideal body weight), or had major metabolic, hepatic, renal, cardiac, pulmonary, hematologic, and central nervous system disease, had a history of allergy, or addiction to alcohol or smoking, or if they took cardiovascular active drugs. All patients had a standardized anesthetic management consisting of premedication with lorazepam 2 mg sublingual 2 hours before induction. On arrival in the anesthetic room a modified V5 EKG lead was attached. Using local anesthesia cannulae were inserted into a peripheral vein and a radial artery and a balloon-tipped, flow-directed thermodilution catheter (American Edwards Co.) was directed into the internal jugular vein. All pressures were recorded by Statham transducers and continuously displayed on a four-channel chart recorder. Twenty minutes after completion of cannulae insertion, baseline measurements, including measurements of cardiac output (thermodilution technique) were made. During the final 60 min before induction each patient

Table 1. Patient characteristics

	Group A (O₂)	Group B (N₂O, O₂)
Age (yrs)	46,2 ± 2,92	47,0 ± 4,15
Weight (kg)	69,3 ± 4,74	65,5 ± 2,32
Height (cm)	170,9 ± 3,8	167,0 ± 2,42
Sex	M6,F4	M8,F2

· Data are mean ± sem (n = 10 in each group).

received 500 ml of intravenous hydroxyethylstarch. Patients were randomly assigned to two groups: Group A consisted of 10 patients who breathed 100% O₂ via a tight-fitting face mask for 5 minutes prior to induction and Group B of 10 patients who breathed 70% N₂O in oxygen for 5 minutes prior to induction. All patients then underwent intravenous induction of anesthesia with propofol 2.5 mg·kg⁻¹ given over 45 seconds followed by vecuronium 100 μg·kg⁻¹. The patients continued to breath their assigned gas mixture spontaneously and, upon disappearance of the eyelash reflex, were manually ventilated with care being taken to avoid increased airway pressure. Four minutes after induction, all patients were intubated within 30 seconds by the same anesthetist and manual ventilation at a rate of 12 per min was begun.

The anesthetic circuit used was a Mapleson C with a tight-fitting face mask and a flow rate of greater than twice the minute volume to prevent rebreathing. End-tidal CO_2 (Ohmeda CO_2 analyzer) and percutaneous oxygen saturation (Nelcor pulse oximeter) were continuously recorded, and remained within normal limits for the duration of the anesthesia.

One, 3, 4.5, and 7 min. after injection, the following were measured: heart rate (HR), systemic systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), mean pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and cardiac output (CO). Systemic vascular resistance (SVR) and stroke volume (SV) were calculated using a standard formula. Data are expressed as mean ± SEM. Statistical analysis within the group was performed by a Friedman test (*P < 0.05) and between the groups by a Mann Whitney Wilcoxon test (+ P < 0.05).

Results

The demographic data of the patients are listed in Table 1. There were no significant differences between the groups with regard to age, weight, or height. The hemodynamic changes following induction are listed in Table 2. There were no statistically

significant differences in baseline values in the two groups.

Group A

Data analysis within the group showed that HR, DAP, PAP, and PCWP did not undergo significant changes at any time while the MAP decreased to 23% below the awake value 3 min after induction (P < 0.05). Immediately after intubation there were transient increases in SAP, DAP, and MAP. CO and SV decreased by 25% and 22%, respectively, after induction (P < 0.05) but without further significant changes after intubation. The SVR remained constant (+4% after 1 minute, −3% after 3 minutes) until intubation, when it increased 51% (P < 0.05).

Group B

Data analysis within the group showed no significant change in HR, MAP, DAP, and PAP after induction, whereas the SAP decreased on average by 18% at 3 minutes (P < 0.05). After intubation slight, but not statistically significant, increases in SAP, MAP, DAP, and PAP occurred. CVP and PCWP increased after induction, reaching statistical significance (respectively 44% and 65%) after intubation. CO and SV decreased immediately after induction (−18% and −22% respectively at 3 min (P < 0.05) but no major changes were seen after intubation. SVR remained stable after induction and increased 44% (P < 0.05) after intubation. There were no significant differences in HR, SAP, MAP, DAP, CVP, CO, SV, and SVR between the two groups (Table 2, Figure 1). PAP, however, was significantly different between the groups after 4.5 and 7 min, as was PCWP at 4.5 min.

Discussion

Previous studies on the cardiovascular effects of an intravenous induction dose of propofol have all documented decreases in systemic arterial pressure (1–8). However, the reasons proposed for the decrease in blood pressure vary between investigators (Table 3). Claeys et al. (1) imply that a decrease in SVR, while CO and SV remained stable, caused the decrease in SAP. Coates et al. (8) and Grounds et al. (5,6) explained the decrease in systemic arterial pressure by decreases in both CO and SVR. Van Aken et al. (2), in contrast, found significant decreases in the CO and SV without concomitant changes in SVR.

Table 2. Hemodynamic Data (mean ± SEM) (n = 10 in each group) during Induction of Anesthesia in Group A (propofol 2.5 mg·kg^{-1}, vecuronium 100 μg·kg^{-1}, 100% O$_2$) and in Group B (propofol 2.5 mg·kg^{-1}, vecuronium 100 μg·kg^{-1}, 70% N$_2$O in O$_2$)

| | | Group A, propofol 2.5 mg/kg, vecuronium 100 μg/kg, 100% O$_2$ | | | | |
		awake	1 min	3 min	4.50 min	7 min
SAP (mm Hg)	x	146.00	120.60	118.20*	175.10	135.00
	Sx	3.32	4.28	9.33	6.08	9.21
DAP (mm Hg)	x	75.40	65.30	60.60	101.50	76.00
	Sx	1.38	2.12	2.15	3.52	4.72
MAP (mm Hg)	x	99.00	83.20	75.90*	129.90	99.00
	Sx	2.23	1.84	2.80	4.78	7.18
PAP (mm Hg)	x	15.40	14.40	14.20	18.80+	15.50+
	Sx	0.82	0.83	1.06	0.81	1.39
HR (beats min^{-1})	x	86.40	89.60	82.60	93.40	87.30
	Sx	3.93	4.89	3.49	3.74	4.01
CVP (mm Hg)	x	4.70	6.20	6.80	7.90*	6.30
	Sx	0.58	0.70	0.84	0.95	0.63
PCWP (mm Hg)	x	6.80	7.60	7.30	10.70+	8.50
	Sx	0.63	0.90	0.72	0.70	1.04
CO (L min^{-1})	x	8.51	6.56*	6.33*	7.23	7.04*
	Sx	0.42	0.27	0.22	0.37	0.33
SV (ml beat^{-1})	x	100.00	75.40*	77.80*	79.00*	81.80
	Sx	5.90	5.60	3.90	5.80	4.40
SVR (dyn·sec·cm^{-5})	x	910.25	950.33	880.95	1378.68*	1076.47
	Sx	57.56	38.73	44.38	90.20	105.42
		Group B, propofol 2.5 mg/kg, vecuronium 100 μg/kg, 70% N$_2$O, 30% O$_2$				
SAP (mm Hg)	x	150.70	127.30	123.70*	164.60	142.30
	Sx	6.78	5.70	9.67	11.38	7.42
DAP (mm Hg)	x	72.90	63.80	69.60	95.60	79.10
	Sx	3.69	3.81	5.03	6.29	4.82
MAP (mm Hg)	x	101.40	88.10	90.40	123.60	103.80
	Sx	4.94	5.26	7.07	7.48	6.11
PAP (mm Hg)	x	20.20	19.20	16.80	25.50+	21.10+
	Sx	2.04	2.00	1.56	2.48	1.56
HR (beats min^{-1})	x	79.40	82.90	83.20	91.10	87.40
	Sx	2.63	2.03	2.72	4.07	3.93
CVP (mm Hg)	x	5.07	6.60	7.30 .	8.20*	8.50*
	Sx	1.23	0.81	0.94	0.90	0.99
PCWP (mm Hg)	x	8.90	8.40	8.80	14.70+*	11.30
	Sx	1.39	1.01	1.18	1.86	1.22
CO (L min^{-1})	x	7.51	6.56	6.15*	6.20*	7.17
	Sx	0.44	0.46	0.42	0.39	0.50
SV (ml beat^{-1})	x	94.50	78.40*	73.70*	68.00*	81.80
	Sx	4.20	3.80	3.80	3.10	3.70
SVR (dyn·sec·cm^{-5})	x	1051.70	1066.92	1112.30	1518.14*	1091.47
	Sx	86.77	135.10	105.78	96.38	77.97

x, mean value.
Sx, standard error of mean.
Comparison within the group *P < 0.05.
Comparison between the groups +P < 0.05.

The purpose of this study was to determine whether N$_2$O alters the specific hemodynamic changes of an induction dose of propofol. In comparison to previous studies (1–8) several methodological features have been incorporated and deserve comment.

First, our patients received a 500-ml infusion of hydroxyethylstarch as a replacement of fluids lost due to restricted preoperative fluid intake. In this way it was hoped that decreases in blood pressure due to fluid depletion were avoided.

Second, all patients prebreathed either 100% oxygen or 70% N$_2$O in oxygen for 5 min using a non-rebreathing circuit and a high fresh gas flow. It has been shown that the ratio between alveolar and inspired N$_2$O is close to unity at 5 minutes (0.93) (12); denitrogenation had therefore, taken place in our subjects.
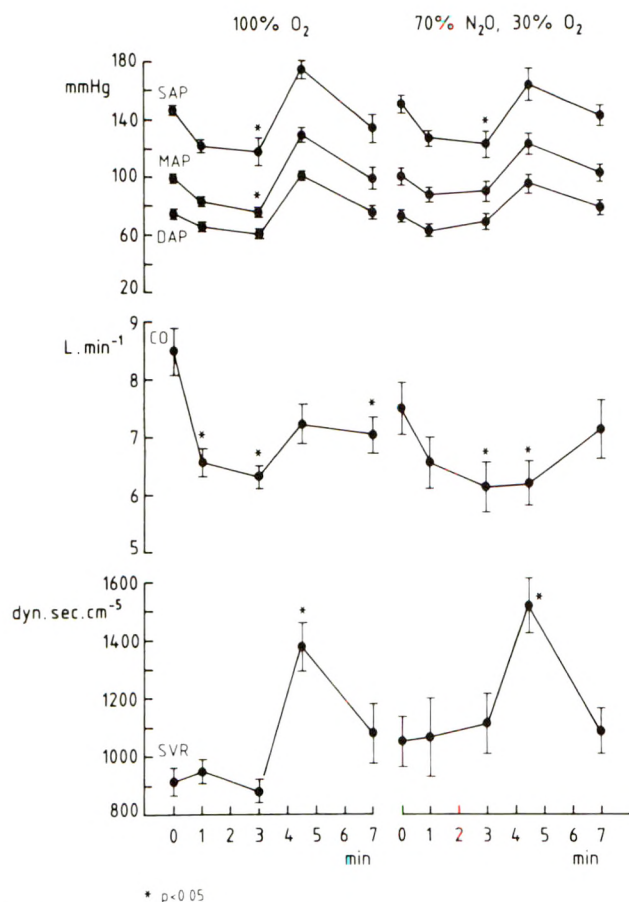
Figure 1. Hemodynamic profiles from 0 to 7 minutes of two groups of patients following injection of propofol 2.5 mg·kg^{-1} (Group A, 100% oxygen; Group B, 70% nitrous oxide in oxygen). Mean ± SEM data. *Significantly ($P < 0.05$) different from baseline values.

Third, PET$_{CO2}$ and SAT$_{O2}$ were continuously monitored and kept within normal levels by the use of manual ventilation via a highflow non-rebreathing circuit. In the studies by Claeys et al. (1, Table 3) the patients breathed room air and in 8 of the 10, apneic periods of 62 to 118 seconds occurred during which carbon dioxide levels were not recorded. Mertzlufft and co-workers (13) found that during such apneic periods considerable increases in PaCO$_2$ of 14 to 18 mm Hg can occur. Increases in PaCO$_2$ above normal levels were recorded in their study 45 minutes after induction. Similarly, Coates et al. (8) in their study recorded increases in PaCO$_2$ from 39.3 mm Hg to 47.9 mm Hg. These changes in PaCO$_2$ may have been important in view of the findings by Cullen et al. (14) that hypercarbia increases CO, SV and HR and decreases SVR in both awake and anesthetized subjects. Indeed, increasing the PaCO$_2$ from 35 to 55 mm Hg doubled the cardiac index in awake subjects (14). The vascular changes associated with hypercarbia were explained by Cullen et al. (14) as indicating a combi-

nation of a direct depressant effect of CO$_2$ on myocardial contractility and a direct dilating effect on peripheral vessels as well as an indirect effect mediated by CO$_2$-induced sympatho-adrenal stimulation. Hypercarbia in the subjects of Claeys et al. (1) may have accounted for their observed decrease in SVR with no significant decrease in CO. Similarly, in the study by Coates et al. (8, Table 3) increases in PaCO$_2$ may have been responsible for the decreases in SVR.

Grounds et al. (5,6), in addition to recording increased CO$_2$ levels, also found decreases in pH. Respiratory acidosis is well known to induce sympathetic activity (15), which may explain why they did not record more profound decreases in the CO. Paulin et al. (7) found decreases of CI ($P < 0.005$) and SVR ($P < 0.050$) in subjects given only propofol 2 mg·kg^{-1} and 100% oxygen. Nevertheless, 8 of their 20 patients had stabilized heart disease, 6 had arterial hypertension, and 2 had unrecognized cardiac insufficiency. In this study PaCO$_2$ varied between 40 to 49.5 mm Hg.

In line with other studies (1–8), Cullen et al. (16) and Samain et al. (17) have reported that propofol resets the baroreflexes to allow slower heart rates at lower arterial pressures. Coupled with this is partial suppression of the usual tachycardia and systolic hypertension (18,19) associated with laryngoscopy and intubation.

In both of our studied groups PAP decreased slightly after induction of anesthesia and increased significantly after intubation. The changes in CVP and PCWP can be attributed in part to an increased intrathoracic pressure due to intubation and assisted ventilation. Increased airway and intrapleural pressures can decrease transmural cardiac filling pressures and lower thoracic venous inflow (20,21).

Vecuronium was used in this study to facilitate tracheal intubation as this drug seems to have minimal effects on cardiovascular parameters (22,23). Nitrous oxide can affect the cardiovascular system in different ways. It can produce a direct myocardial depression (11). This is, however, usually compensated by simultaneous sympathetic activation of the brain nuclei that control β adrenergic activity (24). N$_2$O can also inhibit the uptake of norepinephrine by the lungs, which results in α adrenergic stimulation (11). The net result is little cardiovascular depression at both analgesic and anesthetic partial pressures. Drugs such as narcotics, however, are able to block centrally mediated β adrenergic stimulation of N$_2$O, which results in a different hemodynamic profile when N$_2$O is used in combination with such drugs (25).

In this study a significant reduction in SAP due to

Table 3. Hemodynamic Changes Induced by Propofol as Reported in the Literature. The changes are expressed as percent difference from baseline value.

	SAP	MAP	DAP	CO	SV	SVR	HR	PaCO$_2$
Claeys (1988) bolus 2 mg·kg^{-1} room air spontaneous ventilation	−28%*	−24%*	−19%*	−7%	−17%	−21%*	+10%	expected increase 14–18 mm Hg
Coates (1987) bolus 2 mg·kg^{-1}, 67% N$_2$O in O$_2$ spontaneous ventilation,	−32%*	−24%	−16%	−14%	−13%	−17%	+2%	39.3 mm Hg → 47.9 mm Hg (after 3 min)
Grounds (1985) bolus 2.5 mg·kg^{-1} 100% O$_2$, manual assistance only in case of apnea	−	−32%*	−	−12%*	−14%*	−21%*	=	36.6 mm Hg → 44 mm Hg (after 2 minutes)
Paulin (1987) bolus 2 mg·kg^{-1} 100% O$_2$, manual assistance only in case of apnea	−17%*	−14%*	−12%*	−12%*	−10%*	−7%*	=	variation after 2 min between 40–49.5 mm Hg
Van Aken (1988) bolus 2.4 mg·kg^{-1} 67% N$_2$O in O$_2$ manual normoventilation	−25%*	−20%*	−14%*	−22%*	−22%*	−1%	−2%	38 mm Hg → 40 mm Hg (after 5 minutes)
Carlier (present study) bolus 2.5 mg·kg^{-1}, 100% O$_2$ manual normoventilation	−19%*	−23%*	−19%	−25%*	−22%*	−3%	−4%	ETCO$_2$ 36–40 mm Hg (after 3 minutes)
bolus 2.5 mg·kg^{-1}, 70% N$_2$O in O$_2$ manual normoventilation	−18%*	−10%	−5%	−18%*	−22%*	+5%	+4%	ETCO$_2$ 36–40 mm Hg (after 3 minutes)

a reduction in CO and SV was observed in both groups showing that the simultaneous use of 70% N$_2$O does not change these parameters. SVR, in contrast to findings in other studies (1,5–8), showed only minor changes except after intubation, when an increase due to reflex sympathoadrenal response commonly occurs (18,19). The results of this investigation suggest that the cardiovascular effects of propofol documented in the previous study by Van Aken et al. (2) were not a result of adding N$_2$O.

References

1. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3–9.

2. Van Aken H, Meinshausen E, Prien T, Brüssel T, Heinecke A, Lawin P. The influence of Fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N$_2$O in humans. Anesthesiology 1988;68:157–163.

3. Lippmann M, Paicius R, Gingerich S, et al. A controlled study of the hemodynamic effects of propofol vs thiopental during anesthesia induction. Anesth Analg 1986;65:S89.

4. Meinshausen E, Van Aken H, Prien T, Brüssel T, Heinecke A. Hämodynamik unter Propofol-lachgasnarkose: Auswirkungen einer prämedikation mit Lormetazepam sowie einer additiven Fentanylgabe. Anaesthesist 1987;36:646–652.

5. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction: Comparison of the effects of thiopentane and propofol. Anaesthesia 1985;40:735–740.

6. Grounds RM, Morgan M, Lumley J. Some studies on the properties of the intravenous anaesthetic, propofol—a review. Postgrad Med J 1985;61(3):90–95.

7. Paulin M, Jullian-Papouin H, Roquebert PO, Manelli JC. Effets hémodynamiques du propofol utilisé comme agent unique pour l'induction de l'anesthésie. Ann Fr Anesth Réanim 1987; 6:237–239.

8. Coates DP, Monk CR, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. Anesth Analg 1987;66:64–70.

9. Eisele JH. The cardiovascular effects of N$_2$O. In: Nitrous Oxide, by Eger EI, London: Edward Arnold, 1985:125–56.

10. Eisele JH, Smith NT. Cardiovascular effects of 40 percent N$_2$O in Man. Anesth Analg 1972;51:956–963.

11. Kawamura R, Stanley TH, English JB, Hill GE, Liu WS, Webster LR. Cardiovascular responses to nitrous oxide exposure for two hours in man. Anesth Analg 1980;59:93–99.

12. Parbrook GD. The levels of nitrous oxide analgesia. Br J Anaesth 1967;39:Supplement 74–82.

13. Mertzlufft FO, Rudloff B, Jantzen AH, Brandt L, Dick W. Christiansen-Douglas-Haldane Effekt: Auch in vivo? Anaesthesist 1987;36 Supplement 374.

14. Cullen DJ, Eger EI, Gregory GA. The cardiovascular effects of carbon dioxide in man, conscious and during cyclopropane anesthesia. Anesthesiology 1969;31:407–413.

15. Hornbein TF. Summary of organ vascular responses to acute acidosis. In: "Anesthesia", 2nd edition, by Miller RD. New York, Edinburgh, London, Melbourne: Churchill Livingstone, 1986:1290–1291.

16. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987;66:1115–1120.

17. Samain E, Marty J, Gauzit R, Bouyet I, Couderc E, Desmonts J. Effects of propofol on baroreflex control of heart rate and on sympathetic activity in humans. Anesthesiology 1987;67:A75.

18. Russell WJ, Morris RE, Frewin DB, Drew SE. Changes in plasma catecholamine concentrations during endotracheal intubation. Br J Anaesth 1981;53:837–839.

19. Forbes AM, Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. Br J Anaesth 1970;42:618–624.

20. Downs JB, Douglas ME, Sanfelippo PM, Stanford W, Hodges MR. Ventilatory pattern, intrapleural pressure and cardiac output. Anaesth Analg 1977;56:88–96.

21. Morgan BC, Crawford EW, Guntheroth WG. The hemodynamic effects of changes in blood volume during intermittent positive pressure ventilation. Anesthesiology 1969;30:297–305.

22. Marshall R, McGrath J, Miller R, Docherty J, Lamar JC. Comparison of the cardiovascular actions of ORG NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. Br J Anaesth 1980;52: Supplement 1, 21–31.

23. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (Org NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 1983;58:438–440.

24. Fukunaga AF, Epstein RM. Sympathetic excitation during nitrous oxide-halothane anesthesia in the cat. Anesthesiology 1973;39:23–36.

25. McDermott RW, Stanley Th. The cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 1974;41:89–91.

Clinical Pharmacology of Pipecuronium Bromide

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The neuromuscular blocking and cardiovascular effects of pipecuronium, in doses ranging 2–3 times its ED_{95}, were evaluated in 46 patients during thiopental, fentanyl, N_2O/O_2 anesthesia. The neuromuscular blocking effect of pipecuronium was evaluated by recording of the mechanical twitch of the adductor pollicis muscle in response to stimulation of the ulnar nerve at the wrist. Heart rate, systolic and diastolic blood pressures, and cardiac output were non-invasively measured during the onset of the neuromuscular blockade and compared to a saline control group to separate the effect of anesthesia from those of pipecuronium.

The mean ± SD time from administration of pipecuronium to 90% suppression of the first twitch (T1) of the train–of–four was 2.6 ± 0.8, 2.0 ± 0.6, and 2.1 ± 0.6 min following the 70 μg/kg, 85 μg/kg, and 100 μg/kg dose, respectively. There was no significant difference between the different doses of pipecuronium in the time to 90% suppression of T1. In general, all three doses of pipecuronium provided good to excellent intubating conditions within 3 minutes after its administration. The time from the administration of pipecuronium to 5% recovery of T1 was 52.3 ± 18.2 min in the group given 70 μg/kg. This was significantly longer in patients given 85 μg/kg (71.9 ± 15.7 min) or 100 μg/kg (71.8 ± 22.1 min). Times to the start of recovery of T1 and to 25% recovery of T1 showed a similar significant pattern. In 2/3 of the patients, administration of neostigmine (2.5 mg) resulted in adequate recovery of muscle function within 10 minutes. Only patients with T1 recovery to less than 15% of control or a T4/T1 ratio of zero tended to take longer than 10 minutes for full recovery. Heart rate and systolic and diastolic blood pressures decreased significantly after the induction of anesthesia and during the onset of neuromuscular blockade. The hemodynamic variables, however, were similar between the three pipecuronium groups and a control group (N = 16) that received only saline. Therefore, no cardiovascular changes could be attributed to pipecuronium when compared to the control group. Cardiac output did not change significantly over the time course of the study.

Pipecuronium bromide produces a long–acting, nondepolarizing neuromuscular blockade. A dose of 70 μg/kg can be expected to provide good intubating conditions in 3 minutes with a clinical duration of approximately one hour. Larger doses (85 μg/kg and 100 μg/kg) may shorten the onset time and increase duration on average by 20 minutes. Higher doses are thus best reserved for procedures of long duration. Because no cardiovascular effects were observed with doses ranging from 2–3 times its ED95, pipecuronium can be recommended for patients in whom cardiovascular stability is desired.

Key Words: NEUROMUSCULAR RELAXANTS—pipecuronium.

Pipecuronium bromide is a nondepolarizing neuromuscular blocking agent that is structurally similar to pancuronium and vecuronium. Both pipecuronium and pancuronium have bisquaternary structures but

differ in side chains attached to the steroid nucleus. Pipecuronium has piperazine rings attached at position 2 and 16 of the steroid nucleus, while pancuronium has piperidine rings. Vecuronium, on the other hand, is a monoquaternary compound. The structural modifications in pipecuronium are designed to improve its specificity, leaving the neuromuscular effect intact while reducing the nicotinic side effects on the cardiac vagus nerve. In adults, pipecuronium is approximately 20% more potent than pancuronium with an ED_{95} of approximately 35 μg/kg during intravenous balanced anesthesia (1–3). The purpose of

this investigation was to evaluate the neuromuscular and cardiovascular effects of pipecuronium. To do this, three doses spanning the useful clinical range (2–$3 \times ED_{95}$) were chosen. This study was done during thiopental, fentanyl, N_2O/O_2 anesthesia because of the minimal neuromuscular effects of this anesthetic regimen. To quantitate for the cardiovascular effects of the anesthetic regimen alone, patients similarly anesthetized were given injection of saline instead of pipecuronium.

Methods

Sixty–two ASA physical status I–III patients gave written informed consent to participate in this open–label study approved by our Institutional Review Board. The patients ranged in age from 23 to 63 years, and in weight from 48 to 120 kg. Patients with a history of renal, hepatic, metabolic, or neuromuscular disorders were excluded, as were morbidly obese patients (defined as 100 lb above the ideal body weight). Morphine sulfate (0.1 mg/kg, IM) and atropine (0.4 mg, IM) were administered approximately 1–1.5 hours prior to induction. Anesthesia was induced with thiopental (3–6 mg/kg) and fentanyl (3–6 μg/kg) and was maintained with thiopental (50 mg increments), fentanyl (50 μg increments), and N_2O/O_2 (60/40 ratio).

Neuromuscular blocking evaluation

After the patients lost consciousness, the ulnar nerve was stimulated at the wrist through surface electrodes with train–of–four (TOF) supramaximal square wave impulses of 0.2 msec duration at 2 Hz every 12 seconds. The mechanical twitch response of the adductor pollicis muscle was measured using a Grass FT10 Force Transducer and continuously recorded on a Gould polygraph throughout the operation and for at least 10 minutes following the administration of reversal agent. Resting thumb tension was maintained between 200–300 gm through the study.

After obtaining a stable baseline TOF (approximately 1–2 minutes), 30 patients randomly received either 70 μg/kg (N = 10,) 85 μg/kg (N = 10,) or 100 μg/kg (N = 10) of pipecuronium as a single IV bolus dose injected over 5 seconds. Tracheal intubation was attempted in these patients 1 minute after achieving maximum or 100% neuromuscular blockade.

Sixteen additional patients received 70 μg/kg pipecuronium with intubation attempted at 3 minutes. Intubating conditions were scored on a 1 to 4 scale in which 1 is "excellent" (complete relaxation;) 2 is "good" (slight diaphragmatic movement;) 3 is "poor" (moving vocal cords and bucking;) and 4 is "inadequate" (fighting, tight jaw muscle.) Neuromuscular relaxation was maintained with 5–10 μg/kg doses of pipecuronium administered whenever the first twitch (T1) of the TOF returned to 25% of its baseline value. Toward the end of the surgery, neuromuscular function was allowed to recover spontaneously, as much as clinical circumstances allowed, with residual neuromuscular blockade antagonized as necessary by intravenous injection of neostigmine (2.5 mg) and glycopyrrolate (0.5 mg). N_2O/O_2 was continued until reversal was complete or at least 10 minutes had elapsed.

Hemodynamic evaluation

Heart rate and systolic and diastolic blood pressures were measured using an automated cuff (Dinamapp®) prior to induction of anesthesia, after induction but prior to pipecuronium, and 1 and 2 minutes after the administration of pipecuronium. Cardiac output was measured prior to induction, prior to pipecuronium, and 2 minutes after pipecuronium administration by a noninvasive Doppler technique [Lawrence 3000](4). Cardiac outputs represented the average of two consecutive readings that differed by less than 15%. To distinguish between the effects of anesthesia and pipecuronium on the cardiovascular system, a control group of 16 patients were studied who had the same anesthetic but received saline instead of pipecuronium 2 minutes after they lost consciousness. After the cardiovascular measurements, the control group received another muscle relaxant.

Statistical analysis

Data were analyzed utilizing one way ANOVA, two way ANOVA with repeated measurements on time, and Kruskal–Wallis test. When ANOVA showed a significant difference, the LSD Test was used for further evaluations. A $P < 0.05$ was considered statistically significant. Data are presented as means ± SD.

Results

There were no significant differences in the demographic data except that there were more female

Table 1. Patient Demographics and the Neuromuscular Blocking Effects (Mean ± SD) of Three Different
Doses of Pipecuronium

	70 μg/Kg (N = 26)	85 μg/Kg (N = 10)	100 μg/Kg (N = 10)
Age (yr)	44.6 ± 10.4	38.7 ± 14.1	49.9 ± 10.2
Weight (kg)	69.2 ± 15.2	66.8 ± 12.4	66.3 ± 14.8
Sex	(4 M, 22 F)	(5 M, 5 F)	(3 M, 7 F)
Time to onset of 50% block (min)	1.6 ± 0.6	1.4 ± 0.5	1.4 ± 0.6
Time to onset of 90% block (min)	2.6 ± 0.8	2.0 ± 0.6	2.1 ± 0.6
Time to 100% block (min)	3.7 ± 1.2	3.2 ± 1.1	3.0 ± 0.81
Time to start of recovery (min)	40.1 ± 14.1[a]	57.3 ± 15.6[b]	58.6 ± 15.6[b]
Time to 5% recovery (min)	52.3 ± 18.2[c]	71.9 ± 15.7[d]	71.8 ± 22.1[d]
Time to 25% recovery (min)	69.9 ± 21.6[e]	98.3 ± 18.7[f]	94.6 ± 18.0[f]
Time from 5% to 25% recovery (min)	25.3 ± 8.7	27.4 ± 6.1	28.8 ± 8.0

a & b Different at $P < 0.05$
c & d Different at $P < 0.05$
e & f Different at $P < 0.05$
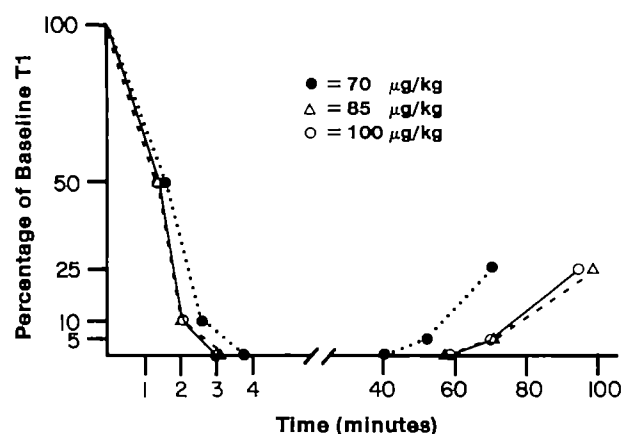
Figure 1. The mean onset and recovery of neuromuscular block-
ade following 3 different doses of pipecuronium.

patients (22 of 26 patients) in the group of patients
given 70 μg/kg (Table 1).

Neuromuscular effects

The neuromuscular blocking effects of 3 different
doses of pipecuronium bromide are summarized in
Table 1 and Figure 1. There was no significant differ-
ence between the dosage groups with respect to time
of onset of blockade. The time to 50% suppression of
T1 was variable among patients but typically occurred
within 2 minutes while time to 90% suppression of T1
was usually reached by 3 minutes. Time to 50% and
90% block of T1 were not significantly shortened by
increasing the dose (Table 1, Figure 1). In only 4 of the
26 patients in the 70-μg/kg-dose group, were more
than 3 minutes required to achieve 90% block of T1,
whereas in one patient in the 100-μg/kg-dose group
and none in the 85-μg/kg-dose group were more than
3 minutes required. When the data for onset of 90%

block after the 85-μg/kg and the 100-μg/kg dose were
pooled (2.06 ± 0.6, N = 20) and compared to onset of
90% block after the 70-μg/kg dose, no significant
difference could be demonstrated (two tailed unpaired
t-test, $P = 0.106$). However, power analysis demon-
strated only a 45% chance of detecting a 20% differ-
ence, if it in fact existed. However, the time from the
administration of pipecuronium to the start of recov-
ery, to 5% and to 25% recovery of T1 was significantly
longer in patients given 85 μg/kg or 100 μg/kg pipecu-
ronium as compared to those who received 70 μg/kg.
No significant difference could be demonstrated be-
tween the 85-μg/kg and 100-μg/kg dosage groups with
respect to the neuromuscular recovery parameters
(Table 1). Intubating conditions were rated good or
excellent in all patients except one who received 85 μg/
kg. Intubating conditions 3 minutes after 70-μg/kg
dose did not differ significantly from the conditions for
those who were intubated after the complete neuro-
muscular blockade had been achieved (Figure 2).
There was no significant difference between the dif-
ferent dosage groups in the degree of residual
neuromuscular blockade prior to, and the rate of
recovery of T1 after the administration of neostig-
mine. When the data for all patients were combined,
the mean percent recovery of T1 was 22.8 ± 13.9
prior to neostigmine administration and 45.8 ± 21.1,
69.7 ± 19.8, 80.7 ± 19.8, and 84.6 ± 18.6 at 2, 5, 8,
and 10 minutes, after neostigmine administration,
respectively. The corresponding mean T4/T1 ratios
were 9.2 ± 10.8, 30.2 ± 18.3, 51.8 ± 21.4, 62.3 ± 20.0,
and 67.0 ± 17.8, respectively. The relationship
between the recovery of T1 and T4/T1 ratio immedi-
ately before and 10 minutes after the administra-
tion of neostigmine (2.5 mg) are depicted in figures
3 and 4. Reversal of neuromuscular block was
successful in all patients. However, the time to full
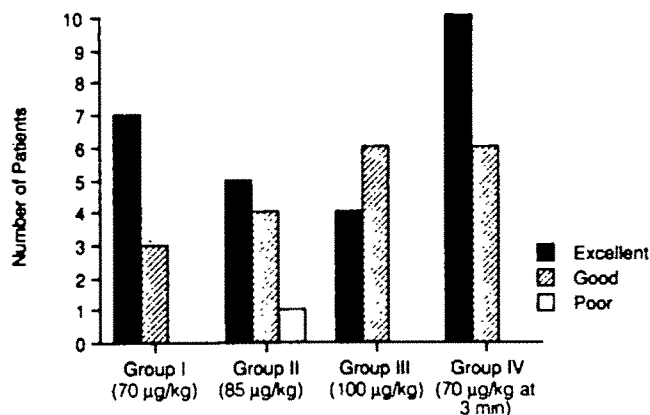
Figure 2. Intubating conditions following pipecuronium. Patients in the first 3 groups (N = 10 each) were intubated at maximum block while patients in the last group (N = 16) were intubated 3 min following pipecuronium administration.
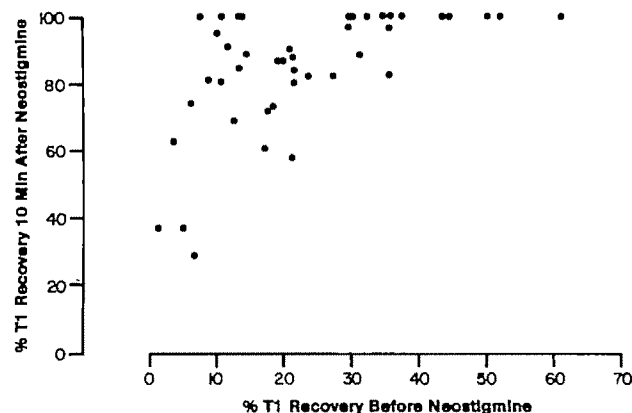
Figure 3. Relationship between the recovery of T1 prior to and 10 min after neostigmine (2.5 mg) administration. Note that 10 min was not sufficient for many patients who had less than 20% recovery of T1 prior to neostigmine administration.

recovery depended on the degree of neuromuscular blockade before neostigmine administration. Ten patients required more than 10 minutes or a second injection of neostigmine for full recovery. These patients had a mean T1 recovery of 11% and a T4/T1 ratio of zero prior to neostigmine administration.

Cardiovascular effects

There was no significant difference between different pipecuronium dose groups and saline group with respect to the cardiovascular data recorded over the time course of the study. Table 2 presents the cardiovascular data by group. While no significant differences between groups were found, there were significant changes in heart rate, systolic and diastolic blood pressures, with the largest changes between awake and post–induction measurements. These changes were common to all groups (Table 2).

T4/T1 Ratio Before Neostigmine
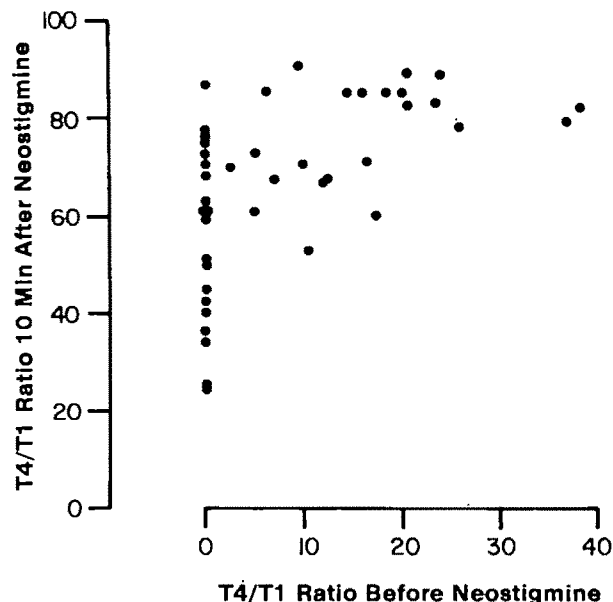
Figure 4. Relationship between T4/T1 ratio prior to and 10 min after neostigmine (2.5 mg) administration.

Discussion

In this study, pipecuronium had a relatively rapid onset of 90% block averaging 2.0 to 2.6 minutes after a single bolus dose of 100 μg/kg or 70 μg/kg, respectively. While patients who received 70 μg/kg dose of pipecuronium tended to have a slower onset of 90% block, the difference between the groups did not reach statistical significance. Pipecuronium provided good to excellent intubating conditions within 3 minutes after 70–100 μg/kg dose. These findings are remarkably similar to those of pancuronium obtained during a similar anesthetic regimen (Meperidine, Thiopental, N_2O) (5). The mean time to peak effect for pancuronium (80 μg/kg) was 207 seconds while the comparable times for pipecuronium (70–85 μg/kg) observed in our study are 222 seconds and 192 seconds. This similarity also holds for the recovery of neuromuscular function. The time to 25% recovery of T1 was found to be 86 ± 13 minutes after pancuronium (80 μg/kg) while for pipecuronium the times were 70 ± 22 minutes and 98 ± 19 minutes after 70 μg/kg and 85 μg/kg, respectively.

As with other muscle relaxants, the speed of recovery of muscle function after neostigmine administration was dependent on the degree of neuromuscular blockade. Ten minutes after the administration of neostigmine (2.5 mg) approximately 2/3 of our patients had either greater than 90% recovery of T1 or a T4/T1 ratio greater than 75%. The mean recovery of T1 and T4/T1 ratio prior to neostigmine administration in these patients was 28.7 ± 14.1% and 9.2 ± 10.8%, respectively. The remaining 15 patients who

Table 2.   Hemodynamic Findings (Mean ± SD) Before and 1 and 2 min After Administration of Pipecuronium or Saline

	Dose (μg/Kg)	Awake	Asleep	1 min	2 min
Heart Rate* (beats/min)	100	82.3 ± 17.5	87.7 ± 13.8	81.6 ± 15.6	80.8 ± 16.7
	85	71.7 ± 16.4	70.7 ± 10.8	66.5 ± 9.4	63.8 ± 8.4
	70	80.9 ± 24.6	92.3 ± 19.1	80.5 ± 16.4	79.5 ± 14.7
	Saline	88.3 ± 20.3	83.8 ± 16.9	79.7 ± 13.2	76.0 ± 13.2
	Mean ± SD	81.6 ± 20.3	83.6 ± 16.9	77.4 ± 14.6	75.1 ± 14.6**
Systolic BP* (mm Hg)	100	138.9 ± 13.8	123.6 ± 22.2	104.7 ± 22.7	108.2 ± 24.4
	85	130.9 ± 15.5	115.2 ± 16.9	105.7 ± 17.0	100.6 ± 17.3
	70	145.9 ± 23.7	125.3 ± 26.4	111.5 ± 19.6	107.9 ± 16.1
	Saline	134.9 ± 20.0	108.5 ± 13.7	105.9 ± 15.2	105.4 ± 15.3
	Mean ± SD	137.3 ± 19.0	117.1 ± 20.3**	106.8 ± 18.0**	105.5 ± 17.8
Diastolic BP* (mm Hg)	100	78.2 ± 7.8	69.9 ± 15.8	62.5 ± 15.8	63.8 ± 15.7
	85	65.0 ± 8.8	58.7 ± 12.2	55.4 ± 12.6	51.6 ± 7.2
	70	73.3 ± 16.0	70.5 ± 16.8	62.4 ± 13.1	60.0 ± 10.1
	Saline	73.0 ± 10.4	61.0 ± 8.9	60.1 ± 9.2	60.0 ± 9.1
	Mean ± SD	72.4 ± 11.6	64.6 ± 13.8**	60.1 ± 12.4	59.0 ± 11.2
Cardiac Output* (L/min)	100	5.2 ± 1.3	4.9 ± 1.2		4.5 ± 1.0
	85	5.3 ± 1.3	5.5 ± 1.6		5.3 ± 1.3
	70	5.9 ± 1.6	5.7 ± 1.5		6.0 ± 2.1
	Saline	6.6 ± 1.9	5.7 ± 1.8		5.4 ± 1.5
	Mean ± SD	5.8 ± 1.7	5.5 ± 1.6		5.3 ± 1.6

* = No difference between groups
** = $P < 0.05$ for difference from previous value

were reversed at a T1 recovery of 13.2 ± 7.0% had a mean T1 recovery of 67.9 ± 19.2% and T4/T1 ratio of 51.4 ± 15.6% ten minutes after neostigmine administration. These patients required either longer than 10 minutes, or a second dose of reversal agent to achieve full recovery of muscle function.

Unlike pancuronium, the cardiovascular effects of pipecuronium were minimal. While blood pressure, heart rate, and cardiac output tended to decline over the course of the study, the changes were similar after injection of pipecuronium and saline placebo. Such cardiovascular changes as did occur were attributed to a continuing effect of the induction drugs, thiopental, and fentanyl, since the patients were not stimulated or given other drugs at this time. Pipecuronium is thus like vecuronium in the absence of cardiovascular effects. It does not cause tachycardia and blood pressure elevation as seen with pancuronium during balanced (6) and halothane anesthesia (7). We compared the cardiovascular effects of pipecuronium to a saline control to allow us to draw conclusions on the direct effects of pipecuronium. It also allows for an estimate of the underlying continuing effect of the anesthetic regimen which were measurable even 5 to 10 minutes after induction. Other studies (6,7) have failed to take these into account so that underlying anesthetic effect were incorporate into the drug effect. Future, well designed, comparative

studies are warranted to determine the advantages and disadvantages of pipecuronium over the other widely used neuromuscular relaxants.

In conclusion, pipecuronium has a relatively rapid onset of effect, providing good to excellent intubating conditions within 3 minutes after the administration of a 70 μg/kg dose. During balanced anesthesia, in doses ranging from 70–100 μg/kg, pipecuronium provides clinical neuromuscular relaxation of 1–2 hours duration. Because 85 and 100 μg/kg took longer to recover, we recommend these higher doses for longer procedures and when a slightly more rapid onset is desired. Full recovery of neuromuscular function after neostigmine (2.5 mg) administration was observed within 10 minutes in the majority of patients. However, patients with less than 20% recovery of T1 prior to the administration of neostigmine may require more than 10 minutes or a second dose of reversal agent to achieve full recovery of muscle function. Pipecuronium can be recommended as a long–acting neuromuscular blocker with predictable neuromuscular properties and an absence of cardiovascular side effects.

References

1. Boros M, Szenohradsky J, Marosi Gy, Tóth I. Comparative clinical study of pipecuronium bromide and pancuronium bromide. Drug Res. 1980;30:389–93.

2. Foldes FF, Nagashima H, Nguyen HD, Weiss R, Goldiner PL. The human cumulative dose–response of pipecuronium bromide under balanced anesthesia. Anesthesiology 1986;65: A116.

3. Azad SS, Goldberg ME, Larijani GE, et al. The dose–response evaluation of pipecuronium bromide in elderly population under balanced anesthesia. Anesthesiology 1987;67:A370.

4. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive doppler determination of card-

iac output in man: Clinical Validation. Circulation 1983;67:593–602.

5. Katz RL. Clinical neuromuscular pharmacology of pancuronium. Anesthesiology 1971;34:550–55.

6. Kerr WJ, Baird WL. Clinical studies on ORG NC 45. Comparison with pancuronium. Br. J. Anaesth. 1982;54:1159–65.

7. Engbaek J, Ording H, Srensen B, Viby-Mogensen J. Cardiac effects of vecuronium and pancuronium during halothane anaesthesia. Br. J. Anaesth. 1983;55:501–5.

Fifty-Seven Years Ago in

Anesthesia & Analgesia

E. I. McKesson: Nitrous oxid anesthesia: a consideration of some associated factors. Anesthesia and Analgesia: 1932;11:54–9.

The author of this article, E. I. McKesson (1881–1936), is of such stature in the history and development of anesthesia in the era between 1907 and 1930 to deserve a subsequent historical note all to himself. The subject of this paper itself is, nevertheless, worthy of the attention of today's anesthetist. Not that it deals with nitrous oxide. It doesn't, except to emphasize that premedication with hyoscine (scopolamine), morphine, and a barbiturate to the point of sedation, never "deep sleep," is absolutely essential prior to administration of nitrous oxide. The "associated factors" are what make the substance of this paper noteworthy. They provide a rare glimpse into the realities of everyday practice of anesthesia and surgery in the 1920s and 1930s. Take, for example, the statement, sure to be enigmatic to most modern anesthetists, that during thyroid surgery "nitrous oxid-oxygen may be administered under pressure to compensate for the partial obstruction to respiration until the vessels are tied." First, this reflects the fact that in this era the main reason for thyroid surgery was hyperthyroidism, not non-toxic nodular goiters. Second, since there was no effective way of controlling hyperthyroidism medically, surgery was resorted to. Third, when resorted to, surgery all too often involved the real risk of potentially lethal intra- or postoperative thyroid storm. Because surgical risk was so substantial, surgery was sometimes delayed until thyroid enlargement had progressed to the point it impaired the airway. Finally, because of the danger of thyroid storm, surgery consisted not of thyroidectomy, but, instead, ligation of the arterial blood supply to the thyroid, often in stages and often using local or, at the most, nitrous oxide anesthesia. Another insight into anesthetic and surgical problems to be gained from this paper centers about intraoperative management of foreign bodies in the trachea or bronchi, including "a tooth, fillings, a wad of gauze or cotton, an adenoid or tonsil, a blood clot, or a chunk of food vomited and inspired." At this time tonsillectomies were routinely done in the sitting position without tracheal intubation. Tracheal intubation was infrequently used, even for major surgery, much less for "simple" T and A's. What to do when aspiration did occur in the days before even rigid, much less fiberoptic, bronchoscopes were available? Why, give oxygen to lighten the depth of anesthesia until the cough reflex was restored. The patient then "usually" coughed out the foreign body. What happened when the patient could not cough out the foreign body is not dwelt upon. No need to. Too obvious. These and other insights offered in this article make us appreciate how far we have come in the last 57 years. No cause for self-congratulation, complacency, or a smug sense of our own superiority, though. How primitive may anesthetists 57 years from now, in 2046, regard our practices today?

A Glossary of Anesthetic Jargon

Edmond I. Eger II, MD

". . . there arises from a bad and unapt formation of words a wonderful obstruction to the mind."
Sir Francis Bacon (1)

The purpose of language is to transmit facts, ideas, and feelings. As with scientific communication in general, clarity and conciseness advance communication in medicine. To convey information quickly, we often resort to slang, jargon, acronyms, and other forms of stylistic shorthand, in the process perhaps losing more than we gain.

Why should we care *how* we communicate, so long as our meaning is clear? If our argot provides a compact and efficient expression of complex concepts, isn't it a desirable and useful tool? Should not our professional language evolve and incorporate new forms of expression? These are valid arguments. The counter arguments are several. The language of anesthesia is not universally accepted and, thus, we communicate best, sometimes only, to our confreres. Our jargon is not always clear or concise and sometimes sabotages the very attempt to be so. The use of slang or jargon may result in ambiguity, imprecision of thought, and an unprofessional image.

The following glossary contains words and phrases overheard in conversations and conferences, or read in our journals. Statements in parentheses or brackets indicate a preferred usage. A similar glossary was prepared by Tolmie and Birch (2).

Aspirate. *The patient was aspirated.* (Secretions were aspirated.) Patients, lungs, and subarachnoid spaces are not aspirated; blood, secretions, or cerebrospinal fluid may be aspirated. The imprecision lies in apply-

ing a technique to the whole patient, rather than the appropriate part.

Bag. *I bagged the patient.* ("I ventilated the lungs of the patient by hand [or manually].)" *To bag* indicates ventilation produced by squeezing a reservoir bag; we bag things (groceries, cement) or animals (a brace of pheasants), not people.

Block. *The patient was blocked.* (A nerve block was used.) The error again lies in applying a technique to the whole patient, rather than a portion of the patient. An additional problem is the arbitrary conversion of a noun to a verb. "Block" may be appropriately used in "brachial block" but may be ambiguous when used in "spinal (or epidural) block." "Spinal block" may mean something quite different to our neurologist colleagues who may get nervous when patients have a "spinal block." In addition, Greene has made a case for not using "block" at all, at least as it is applied to the central nervous system (3). He argues that we would be served better by substituting the word "anesthesia" when nerve transmission is interrupted (*e.g.*, spinal or epidural anesthesia with lidocaine,) or "analgesia" when only analgesia is produced (*e.g.*, with a narcotic placed in the epidural or subarachnoid space.) Thus he would eschew the use of "block" except where morphologic obstruction occurs; *and* he would have us carefully distinguish between the meaning of "anesthesia" and "analgesia." His approach eliminates ambiguity and improves precision.

Bolused. *The man was bolused with 600 ml of fluid.* (600 ml of fluid were given.) The problem (with this and some subsequent words) again is the noun-to-a-verb (*bolused*) conversion. Other examples are *lesion* to *lesioned*, *tracheostomy* to *tracheostomized*, *tracheotomy* to *trached*, *shunt* to *shunted*, *dose* to *dosed*, *tachycardia* to *taching*, and *bradycardia* to *bradied*. (Also see *block*.)

Breathed. *I breathed the patient 12 times a minute.* (I ventilated the lungs 12 times a minute.) Considered

an alternative to *ventilate, breathed* unfortunately implies inspiration *by* the anesthetist. Worse is the statement: *I breathed* (or *blew* or *gassed*) *the patient down.* (I anesthetized the patient.)

Code. *The patient was coded.* (The patient had a cardiac arrest; and we applied CPR.) The word "code" derives from the now–universal use of "code–blue" to announce the development of cardiac arrest and, sometimes, treatment of the arrest.

Crashed (or *blitzed*). *The patient was crashed.* (We induced anesthesia rapidly.) *Crashed* denotes the rapid induction of anesthesia, usually with agents given intravenously. The term also implies the rapid insertion of an endotracheal tube.

Deep. *I carried the patient deep throughout the case.* (I maintained a deep level of anesthesia throughout the surgical procedure.) *Deep* and *light* are so ingrained in our vocabulary to indicate the level of anesthesia that their use has become an accepted (and proper) part of the language of our specialty. The problem is in their application. Both are adjectives, not adverbs: both describe a thing (deep blue sea) or state (deep level of anesthesia) not an act (such as jump or carry.) You cannot "carry deep," but you may maintain "a deep level of anesthesia."

Difficult airway. *The patient was a difficult airway.* (The patient's airway was difficult to maintain.) The problem here is an equivalence state that defies reality, and the substitution of a whole for a part. Variants include: *He was a full stomach,* (He had a full stomach.) Or: *He was a difficult intubation.* (Intubation was difficult.)

Digitalized. *We digitalized the patient.* (The patient was given digitalis.) The intent is to convey that digitalis was administered, and this usage is becoming accepted. However, ambiguity may result. *We digitalized the patient* could imply a rectal examination, or a binary transformation of the patient.

Down. *We put the patient down.* (We anesthetized the patient.) The literal *vs.* intended meaning of "down" creates ambiguity. Another misuse: *The patient bradied down.* (The patient developed bradycardia.) Beyond the metamorphosis of *bradied* (see *bolused,*) the context makes *down* redundant. *Down* also has a spatial connotation that leads to ambiguity (also see *dropped, fall,* and *rose.*)

Dropped. *She dropped her Pao$_2$ from 75 to 58.* (Her Pao$_2$ decreased from 75 to 58.) It is unlikely that the patient actively produced the decrease in Pao$_2$. *Dropped* is being used to indicate *decreased*. Only objects drop; quantities decrease. A variant is *cut*: *Then I cut her down to 1%.* (I then decreased the concentration to 1%.)

Estimate. *Blood glucose concentrations were estimated.* (Blood glucose concentrations were measured.) Although equated with *measured, estimated* implies that the concentrations of glucose were guessed rather than accurately determined.

Extubate. *We extubated the patient.* (We removed the endotracheal tube.) *Extubate* is a perfectly good word, but here it is applied to the whole patient. The problem is doubled in the following: *The patient extubated himself.* (The patient removed his own endotracheal tube.) Parenthetically, *tracheal* rather than *endotracheal* might be used because one assumes that no exotracheal tube exists. Variants on the removal theme are: *We pulled the tube. We sucked out the patient.* More compact, but ambiguous and incorrect is: *We aspirated the patient.* (We aspirated secretions from the trachea.)

Fall. *The blood pressure fell.* (The blood pressure decreased.) *Fell* denotes downward movement in space. Books fall to the floor and meteorites fall to Earth. Physiologic variables do not fall. Blood pressure and heart rate may decrease, but do not fall. (Also see *dropped* and *rose.*)

Fast. *The patient was fasted.* (The patient fasted.) The verb *fast* is intransitive. That is, it cannot carry action from an agent (doer) to another agent or object (receiver), as in *I dropped the ball.* I fast, you fast or they fast, but we cannot fast another person. We may starve them, however.

Gases. The misuses are several. *Blood gases were measured.* (Blood gas *partial pressures* were measured.) *Blood gases were normal.* This asserts that no abnormal gases (*e.g.,* xenon) were present. (Blood gas partial pressures were normal.) *Plasma electrolytes were normal* presents the same problem, unless one is searching for an electrolyte not usually found in human blood. (Electrolyte concentrations in plasma were normal.) Another misuse: *Blood gases were sampled from the artery.* (Arterial blood samples were obtained for measurement of gas tensions.) Gases are not sampled from an artery.

Induced. *We induced the patient.* This common expres-

sion exemplifies the inaccuracy of verbal shorthand and, in fact, is no shorter than the correct statement. (We induced anesthesia.) *Anesthesia was induced with thiopental and succinylcholine.* Succinylcholine does not induce anesthesia. (Anesthesia was induced using thiopental; and muscle relaxation was provided with succinylcholine.)

Intubate. *We intubated her.* Or worse: *We tubed the patient.* (We intubated the trachea. Or: We inserted an endotracheal tube.) The incorrect statements could mean that the patient was placed in a tube, or was made into a tube, or that a tube was placed in a convenient cavity. Sometimes, it is not the patient who is *intubated: We did a fiberoptic intubation.* The statement literally indicates that the fiberoptic instrument was intubated. (We used a fiberoptic bronchoscope to facilitate intubation.)

Lined. *He was lined to get an arterial trace.* (We inserted an intra-arterial catheter to obtain arterial blood pressure.) The patient who has intravenous or intra-arterial catheters inserted is not *lined. Lined* suggests an artistic tone. Zauder has cleverly detailed the case against *lines* (4).

Mask induction. *Mask induction was begun.* Was the mask to be anesthetized? (We induced anesthesia via a mask.) This beauty contains two errors: *We masked the patient down.* (We induced anesthesia via a mask.)

Mask ventilate (or *delivered gas X.*) *We mask ventilated.* Or: *I gave her mask halothane.* One hopes that the mask itself wasn't ventilated. (We ventilated via a mask. Or: I administered halothane via a mask.) Similar to *mask induction,* the usage is intended to indicate ventilation or administration of an anesthetic via a mask, but the literal meaning is that the mask was ventilated or was the type of halothane. A variant of *mask ventilating* (or *bagging*) is *hand ventilate. I hand ventilated.* (I ventilated the patient's lungs by hand.) Most of us would not ventilate a hand.

Nauseous. *Patients become nauseous after anesthesia.* (Patients become nauseated after anesthesia.) They do not, by and large, become nauseous, *i.e.,* cause nausea in others.

On. *The patient was put on a ventilator.* Clearly, this would be an uncomfortable position for the patient. (The patient's lungs were mechanically ventilated.) *He was breathing spontaneously on isoflurane.* (He ventilated spontaneously while breathing isoflurane.) *On* is widely used to indicate the application of some

management. The potential for misapplication is enormous. *On nasal prongs* is a particularly egregious variant: *We put the patient on 5 liters of nasal prongs.* (We gave 5 liters of oxygen via nasal prongs.) *He was put on drug X.* (He was given drug X.)

Post– and Pre–. *Post–* and *Pre–* are prefixes used before adjectives, not nouns, *e.g.,* post–operative, not post–operation. One should not use post–halothane or post–epidural. Similarly, pre–operative, not pre–operation medication. What ever happened to *before* and *after?*

Pure. *We gave pure oxygen.* (We gave oxygen.) If we give *pure oxygen,* does this imply that others might not? Do we use *pure* because we desire to appear virtuous? It also is not usually necessary to say: *We gave 100% oxygen.* (We gave oxygen.)

Pushed. *We pushed the Pentothal.* (We administered Pentothal. Better yet: We administered thiopental.) *Pushed* connotes administration of drugs or fluids, often in amounts that are greater than those usually given.

Reversed. *We reversed the pancuronium* (*or fentanyl or heparin, etc.*) (We antagonized the effect of the pancuronium.) The intent is to indicate antagonism or reversal of an effect. The error is sometimes compounded by applying the term to the patient rather than the drug: *We reversed the patient.* (We antagonized the paralysis.)

Rose. *The blood pressure rose.* (The blood pressure increased.) The past tense of raise, *rose* denotes upward movement in space. The smoke rose, but the blood pressure increased. (Also see *dropped* and *fall.*)

Spiked. *The patient spiked a temperature.* (The patient had a temperature spike.) The original statement implies that the temperature was nailed by the patient.

Stabilized. *The patient was stabilized in the ICU.* (The patient's cardiovascular condition was supported—or stabilized—in the ICU.) The term is applied, incorrectly, to the whole patient rather than a specific condition or system. A variant is: *The patient was stabilized out.*

Started (or stopped.) *We started the halothane.* (We started the administration of halothane.) *Started* (or *stopped*) indicates initiation (or termination) of some therapy. Usually we start a process, not an object.

(in) Trendelenburg. *We put the patient in Trendelenburg.* Alas, poor Freidrich. (We put the patient in the Trendelenburg position.)

With. *She was exchanging well with a nasal airway.* Was the conversation recorded? (She ventilated easily through a nasal airway. Or: Insertion of a nasal airway permitted adequate ventilation.) This is a variant of *on*. However, I rather like the image of a patient holding a conversation with a nasal airway. *The trachea was intubated with succinylcholine.* (Administration of succinylcholine facilitated intubation of the trachea.) A tube, not succinylcholine, was placed in the trachea.

Anesthesiologists do use jargon in their writing, and use it still more when they speak. Surely, we do not wish our surgical and internist colleagues to believe that a function of an anesthesiologist is to *bag patients.* Being attentive to common errors might abolish these inappropriate uses of language. Otherwise, "... words ... [may] ... throw everythin into confusion, and lead mankind into vain an innumerable controversies and fallicies" (1).

References

1. Sir Francis Bacon. The new organon and related writing Anderson FH ed. New York: Liberal Arts Press, 1960.
2. Tolmie JD, Birch AA. Anesthesia for the uninterested. Secor Edition. Rockville, MD: Aspen Publishers, 1986:247–56.
3. Greene NM. Another tower of Babel? Schmerz–Pain–Douleu 1987;3:89–91.
4. Zauder HL. Medical jargon—A few lines about "lines." Ane thesiology 1980;53:271.

Effect of Midazolam Pretreatment on the Intravenous Toxicity of Lidocaine with and without Epinephrine in Rats

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TORBINER ML, YAGIELA JA, MITO RS. Effect of midazolam pretreatment on the intravenous toxicity of lidocaine with and without epinephrine in rats. Anesth Analg 1989;68:744-9.

The effect of the benzodiazepine midazolam on the intravenous toxicity of lidocaine with and without epinephrine was studied in male Sprague-Dawley rats. Test rats with and control rats without midazolam premedication (2.5 mg/kg intraperitoneally, 10% of the median dose that caused loss of the righting reflex in a third group of rats) were given 2% lidocaine with and without 10 μg/ml epinephrine intravenously in doses sufficient to construct log-dose response curves for both convulsant and lethal responses. In control rats the median convulsant dose (CD50) of lidocaine was 15.2 mg/kg given alone and 10.9 mg/kg with epinephrine (a statistically significant difference); respective values for the median lethal dose (LD50) were 26.4 and 18.5 mg/kg (also statistically significant). While epinephrine enhanced lidocaine seizure activity and lethality by approximately 50%, midazolam almost completely prevented lidocaine-induced convulsions but had no significant effect on mortality.

Key Words: ANESTHETICS, LOCAL—lidocaine. TOXICITY, LOCAL ANESTHETICS—lidocaine. HYPNOTICS, BENZODIAZEPINES—midazolam.

Systemic toxic reactions to local anesthetics are brought about by absolute overdosage, rapid absorption from the injection site, and, most commonly, inadvertent intravascular injection (1). Whereas central nervous system (CNS) excitation leading to seizures is a common manifestation of local anesthetic toxicity, in the absence of effective treatment death is usually the result of CNS depression and respiratory arrest.

Many investigators have documented the ability of benzodiazepines to increase the threshold for systemic reactions to local anesthetics (2–10). For instance, de Jong and Heavner recorded a two-thirds increase in the median convulsant dose (CD50) in monkeys after preadministration of diazepam intramuscularly and also demonstrated the ability of intravenous diazepam to attenuate and/or terminate lidocaine-induced seizures (2). Studies by Aldrete and Daniel (3) and by Ausinsch et al. (4) independently confirmed the beneficial influence of benzodiazepines on local anesthetic toxicity. More recently,

Vatashsky and Aronson found flunitrazepam to be more effective than diazepam in preventing seizures induced by local anesthetics (5).

With the exception of a single study conducted on mice (6) there is little information on the possible ability of midazolam to increase the threshold for systemic reactions to local anesthetics. Additionally, local anesthetics often include epinephrine when used for nerve blocks, infiltration, or epidural injection, yet there is a dearth of information on the interaction of benzodiazepines with local anesthetics containing epinephrine.

This investigation was undertaken to determine the effect of midazolam pretreatment on the intravenous toxicity of lidocaine with and without epinephrine.

Methods

This study was approved by the Animal Rights Investigational Committee of the University of California, Los Angeles. Male Sprague-Dawley rats weighing between 100 and 140 g were housed in a light-controlled and temperature-controlled animal care facility. All injections were given between the hours of 2:00 p.m. and 6:00 p.m. Animals fasted from 6:00 p.m. the day prior to their use in the study; water

Table 1. Lidocaine-Induced Seizures in Control and Midazolam-Pretreated Animals

Dose (mg/kg)	Control*	Midazolam pretreatment
Lidocaine (2%)		
13.3	2/5	—
20	7/10	0/5
30	9/10	0/10
45	7/9†	0/9
68	—	2/5
Lidocaine (2%) with epinephrine		
(10 μg/ml)		
6.7	0/5	—
10	4/10	0/5
15	9/10	0/10
22.5	9/9	0/10
34	—	0/5

*Animals died/animals tested.

†Sudden death may have prevented the expression of seizure activity in 2 animals. These data were not used in the construction of Figures 2 or 3, or in subsequent analyses.

Figure 1. Loss of righting reflex in response to intraperitoneal midazolam. Figures in parentheses indicate the number of animals responding versus the number tested at each dose. ED50 = median effective dose for loss of righting reflex.

was supplied ad libitum. Each rat was randomly assigned to a treatment group and only used once (i.e., given a single dose of test drug).

The intraperitoneal dose of midazolam hydrochloride (5 mg/ml, Roche Laboratories) that produced loss of righting reflex in 50% of the animals (ED50) was determined by probit analysis of a standard dose-response curve involving the responses of 37 rats. Loss of righting ability was assessed by placing the animal on its back every 3 minutes after the injection of midazolam; rats that were not able to right themselves within 5 seconds of this maneuver were considered to have lost their righting ability. The time from injection to loss of righting reflex and the duration of the loss were also recorded in order to estimate the time to peak CNS depressant effect. Subsequent animals in the study were given midazolam intraperitoneally at a dose approximating 10% of the ED50.

Ten minutes after midazolam pretreatment (the time interval that corresponded to the peak sedative effect of midazolam), animals were placed in a commercial restraining device, and 2% lidocaine hydrochloride with and without 1:100,000 epinephrine (Astra Pharmaceutical Products, Inc.) were injected into a tail vein in doses sufficient to construct log-dose response curves for both convulsant and acute lethal responses (see Table 1 for the actual doses and number of animals used). Animals in the control groups received similar doses of local anesthetic without benzodiazepine pretreatment. Intravenous injections were made only after aspiration of blood into the syringe was obtained. Immediately after injection of lidocaine with or without epinephrine

each rat was removed from the restraining device and monitored for a period of 60 minutes for convulsions and death. Determination of the incidence of convulsions was based upon the observation of tonic contractions (arching of neck, stiffening of tail) and/or clonic seizures (whole-body jerks or bursts of running motions). Death was indicated by the cessation of respiratory efforts.

Dose-response relationships were analyzed according to the description by Finney (11). A separate log dose-probit regression line was determined for each drug treatment using the maximum likelihood method, in which weighting coefficients are applied in a reiterative process to determine the line of best fit. The median response (ED50, CD50, or LD50, depending on the measured response) and its exact 95% confidence limits were then calculated off of the regression results. The relative potencies (potency ratios and exact 95% confidence limits) of compared drug treatments were determined by parallel linear regression (also after probit transformation of the quantal response data). Tests for homogeneity, regression, and parallelism of regression were performed by χ^2 analysis ($P < 0.05$ being considered significant).

Results

Figure 1 illustrates the effect of midazolam on the righting reflex. Within 2 minutes after intraperitoneal injection, spontaneous activity of all the animals decreased markedly, as evidenced by a slowing of movement and decreased vocalizations when handled. Maximum depression occurred 10 to 15 minutes after midazolam injection, with many of the animals losing use of the hind legs. The righting reflex was

Table 2. Lidocaine-Induced Deaths in Control and
Midazolam-Pretreated Animals

Dose (mg/kg)	Control	Midazolam pretreatment*
Lidocaine (2%)		
13.3	0/5	—
20	2/10	0/5
30	6/10	6/10
45	9/9	8/9
68	—	5/5
Lidocaine (2%) with epinephrine (10 μg/ml)		
6.7	0/5	—
10	0/10	0/5
15	1/10	2/10
22.5	8/9	8/10
34	—	5/5

*Animals died/animals tested.

Figure 2. Control responses to lidocaine with and without epinephrine. The slopes of the probit regression lines are positively and significantly correlated with the log dose but not significantly different from each other at the .05 level. Median convulsant and median lethal doses (CD50s and LD50s) and the potency ratios derived from these curves (the latter represented by the horizontal displacement of the regression lines) and from Figures 3 and 4 are listed in Tables 2, 3, and 4.

Figure 3. Lack of influence of midazolam pretreatment on the lethality of lidocaine.

also lost by this time in rats showing this response (19 of 37 animals tested). Approximately 30 minutes after the injection the majority of animals began to show signs of recovery, as indicated by return of the righting reflex and/or increased exploratory behavior. Based on these results a midazolam dose of 2.5 mg/kg, approximately one tenth the ED50 for loss of righting reflex (which was 24.3 mg/kg, with 95% confidence limits of 19.4 to 30.6 mg/kg), was used for premedicating rats before injection of the local anesthetic. Even at these lower doses the animals showed signs of significant CNS depression, including a lack of resistance or vocalization when placed in the restraining device and injected with the local anesthetic.

Responses in the control group to lidocaine administration were dose related. At low doses most animals exhibited no obvious effects from the injection other than sedation. At the higher doses convulsions became prominent. Seizures lasted approximately 15 seconds and were followed by either quick recovery (10 animals, most regaining locomotion within 2 minutes) or death (15 animals). In 2 rats given the highest dose for the group (45 mg/kg) death occurred almost instantaneously and without observable seizures. The convulsant and lethal responses to intravenous lidocaine are listed in Tables 1 and 2. The same general pattern of response was noted with lidocaine and epinephrine but at lower doses of the local anesthetic (Tables 1 and 2). Figure 2 illustrates how the addition of epinephrine increased the toxicity of lidocaine in animals not pretreated with midazolam.

Rats premedicated with midazolam generally followed one of three patterns after injection of lidocaine: 1) prolonged sedation, 2) a state resembling

general anesthesia during which the animals slept and were unresponsive to stimulation but from which they recovered, and 3) sudden death without overt evidence of convulsions. These general patterns of behavior were again unaffected by the coadministration of epinephrine.

Only 2 of 59 rats premedicated with midazolam convulsed when given the local anesthetic (versus 47 of 68 in the controls), which precluded establishment of a meaningful dose-response relation and calculation of a CD50. Figure 3 displays the effect of midazolam on the lethality of lidocaine without epinephrine, while Figure 4 does the same for lidocaine with epinephrine. It is clear from these figures that midazolam had no significant influence on lethality with either local anesthetic preparation.

In summary (Table 3), epinephrine significantly reduced the CD50 and LD50 for lidocaine, whereas midazolam abolished convulsant responses to lido-
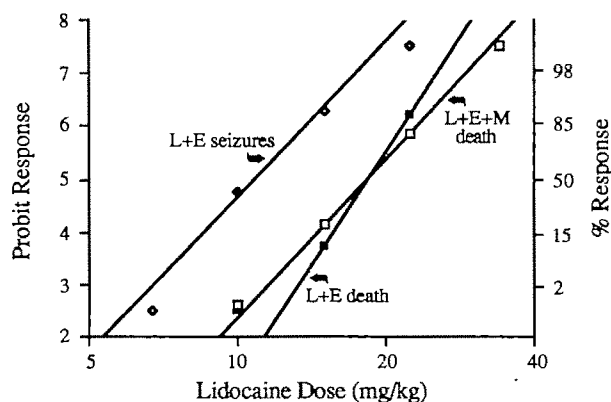
Figure 4. Lack of influence of midazolam pretreatment on the lethality of lidocaine with epinephrine.

caine with or without epinephrine but was ineffective in preventing death.

Discussion

Until recently the most commonly used benzodiazepine for intravenous sedation and anesthesia was diazepam. Midazolam enjoys several advantages over diazepam, including less venous irritation on injection and less postoperative venous sequelae, a shorter elimination half-life, and possibly a more profound amnestic effect (12–16). These advantages are tempered by recent reports of fatalities associated with the use of midazolam for "conscious" sedation, particularly in elderly patients and in situations where monitoring may not have been ideal (17). With respect to seizure control, midazolam has been shown to be effective clinically in terminating convulsions associated with alcohol withdrawal and with various forms of epilepsy (18).

Our results support the findings of de Jong and Bonin (6) on the salutary effect of midazolam pretreatment on local anesthetic-induced seizures in mice. The ability of midazolam as an anticonvulsant relative to other benzodiazepines, however, has not been fully established. In their study de Jong and Bonin compared midazolam, diazepam, and lorazepam at equal doses (1 mg/kg) injected intramuscularly. Midazolam was found to be the most effective anticonvulsant, but their study design neglected potential differences in potency and intramuscular absorption (19,20). A comparative evaluation of the benzodiazepines would seem to require the use of equally sedative (or anesthetic) doses adjusted as necessary to account for any differences in absorption.

While midazolam proved effective in preventing convulsions in the present study, we found that it had essentially no influence on lidocaine lethality.

This conclusion is in contrast to that of de Jong and Bonin. In their study the LD50 of several local anesthetics administered intraperitoneally was increased by the prior intramuscular administration of benzodiazepines. The differences between their results and ours might be attributed to the different routes of administration used for the local anesthetics or to species-specific differences. However, one must question the previous authors' conclusion, at least with respect to lidocaine, because they used historical data for controls in their study, and the actual differences in LD50 were quite modest (less than 11% increase in LD50 for both diazepam and midazolam pretreatment). The protective effect of benzodiazepines against bupivacaine lethality (approximately a 35% increase in LD50) was more substantial. As postulated by de Jong and Bonin, this benefit may be because bupivacaine produces severe cardiac toxicity that is preventable by benzodiazepine premedication. Alternatively, suppression of seizures may be more important with local anesthetics that elicit longer lasting and/or more pronounced muscular hyperactivity than does lidocaine. Since epinephrine appears to enhance local anesthetic lethality (discussed below), inhibition of catecholamine release from the adrenal medulla by a midazolam-induced sedative-antianxiety effect cannot be discounted.

In our control animals the LD50 of lidocaine was more than 70% greater than the CD50 for both lidocaine with and without epinephrine. Thus, the margin of safety between convulsions and death was greater than that reported for mice (6,21). One reason for this discrepancy may be that the smaller mice are unable to tolerate even brief episodes of anoxia. As one moves up in size the ability to withstand short periods of hypoxia, hypercarbia, and/or lactic acidosis may increase, thus lessening the threat of seizures adding to the respiratory depression caused by the lidocaine, which has been shown to be the cause of death in studies of this kind (22). It is not surprising then that other investigators have observed progressively wider margins of safety between convulsant and lethal doses in larger animals, including cats and monkeys (23,24).

The apparent ability of midazolam to block lidocaine seizures without reducing lethality represents a potential concern if the data from this study are applicable to humans. In situations where respiratory competence is not being routinely and continuously monitored by a professional whose sole responsibility is the anesthetic management of the patient, premedication with a benzodiazepine could conceivably compromise patient safety by preventing or masking valuable warning signs and symptoms of impending

Table 3. Effects of Midazolam on Lidocaine-Induced Seizures (CD50) and Lethality (LD50)

	Control		Midazolam pretreatment		
	CD50	LD50	CD50	LD50	Potency ratio*
Lidocaine	15.2	26.4	—	29.5	0.88
	(0–20.4)	(22.4–31.4)		(22.8–36.3)	(0.69–1.15)
Lidocaine with epinephrine	10.9	18.5	—	18.4	1.01
	(8.8–12.9)	(15.9–21.7)		(15.3–22.1)	(0.82–1.25)
Potency ratio†	1.55‡	1.42‡	—	1.63‡	
	(1.02–2.10)	(1.12–1.76)		(1.26–2.07)	

Values in parentheses indicate the 95% confidence limits for each number given above.
*Lethal potency ratio of control/midazolam.
†Lidocaine/lidocaine with epinephrine.
‡Ratio significantly greater than 1 ($P < 0.05$).

lidocaine overdose (including confusion, dizziness, circumoral numbness, tinnitus, restlessness, slurred speech, nystagmus, and visual disturbances), or the seizures themselves, any of which might prompt the clinician into taking appropriate action, such as stopping further administration, instituting meticulous monitoring of the patient, and providing ventilatory support. This concern, of course, does not apply to the therapeutic use of a benzodiazepine in the treatment of lidocaine-induced seizures. (Although not addressed in this study, it is widely accepted that benzodiazepines are drugs of first choice to terminate seizures in an emergency.) It is also possible that the risk to benefit ratio would still favor the judicious use of benzodiazepine premedication in older and/or debilitated patients who are potentially at special risk of local anesthetic seizures (25).

It seems that a review of what benzodiazepines are actually protecting patients from during regional anesthesia is in order. In our study, as well as in those of others, the dose of benzodiazepines used to prevent seizure activity may be sufficient to accentuate the respiratory depression of the local anesthetic, thus voiding whatever benefits are obtained by blocking convulsions. Only by examining a wide range of doses and quantifying physiologic responses will it be possible to develop a full appreciation of the interaction of midazolam and other benzodiazepines with local anesthetic toxicity.

Finally, as described in previous studies (22,26), the intravenous injection of lidocaine in combination with epinephrine significantly lowers the threshold for toxic reactions to the local anesthetic. The probable reason for this potentiation is that epinephrine causes a greater proportion of the lidocaine to enter the CNS (27). The use of epinephrine in combination with local anesthetics has been advocated primarily due to the ability of epinephrine to retard the systemic absorption of the local anesthetic. This slower absorption provides a longer duration of anesthesia and, presumably, a decreased incidence of toxic re-

actions. Indeed, the currently accepted maximum dosage of lidocaine is approximately 60% higher when epinephrine is added to the solution. It is now apparent that should accidental intravascular injection occur, which is believed to be the most common cause of toxic reactions to lidocaine, the presence of the epinephrine may augment the threat of an adverse response.

References

1. Covino BG. Systemic toxicity of local anesthetic agents. Anesth Analg 1978;57:387–8.
2. de Jong RH, Heavner JE. Diazepam prevents and aborts lidocaine convulsions in monkeys. Anesthesiology 1974;41:226–30.
3. Aldrete JA, Daniel WO. Evaluation of premedicants as protective agents against convulsive (LD50) doses of local anesthetic agents in rats. Anesth Analg 1971;50:127–30.
4. Ausinsch B, Malagodi MH, Munson ES. Diazepam in the prophylaxis of lignocaine seizures. Br J Anaesth 1976;48:309–13.
5. Vatashsky E, Aronson HB. Flunitrazepam protects mice against lidocaine and bupivacaine-induced convulsions. Can Anaesth Soc J 1983;30:32–6.
6. de Jong RH, Bonin JD. Benzodiazepines protect mice from local anesthetic convulsions and deaths. Anesth Analg 1981;60:385–9.
7. de Jong RH, Heavner JE. Local anesthetic seizure prevention: diazepam versus pentobarbital. Anesthesiology 1972;36:449–57.
8. de Jong RH, Heavner JE. Diazepam prevents local anesthetic seizures. Anesthesiology 1971;34:523–31.
9. Munson ES, Wagman IH. Diazepam treatment of local anesthetic-induced seizures. Anesthesiology 1972;37:523–7.
10. Vatashsky E, Beilin B, Aronson HB, Weinstock M. Oral flunitrazepam in the prevention of local anaesthetic-induced convulsions in mice. Can Anaesth Soc J 1984;31:646–9.
11. Finney DJ. Probit analysis. Cambridge: Cambridge University Press, 1952:48–72.
12. Barclay JK, Hunter KMacD, Mcmillan W. Midazolam and diazepam compared as sedatives for outpatient surgery under local analgesia. Oral Surg Oral Med Oral Pathol 1985;59:349–55.
13. Aun C, Flynn PJ, Richards J, Major E. A comparison of midazolam and diazepam for intravenous sedation in dentistry. Anaesthesia 1984;39:589–93.

14. Ochs MW, Tucker MR, White RP jr. A comparison of amnesia in outpatients sedated with midazolam or diazepam alone or in combination with fentanyl during oral surgery. J Am Dent Assoc 1986;113:894-7.

15. Tucker MR, Ochs MW, White RP jr. Arterial blood gas levels after midazolam or diazepam administration with or without fentanyl as an intravenous sedative for outpatient surgical procedures. J Oral Maxillofac Surg 1986;44:688-92.

16. Wood N, Sheikh A. Midazolam and diazepam for minor oral surgery. Br Dent J 1986;160:9-12.

17. Versed comparative adverse reaction study to Valium is underway: FDA has received 70 reports of cardiorespiratory events linked to Versed use. F-D-C Reports May 9, 1988.

18. Galvin GM, Jelinek GA. Midazolam: an effective intravenous agent for seizure control. Arch Emerg Med 1987;4:169-72.

19. Van De Velde A, Camu A, Claeys MA. Midazolam for intramuscular premedication: dose-effect relationships compared to diazepam, fentanyl and fentanyl-droperidol in placebo controlled study. Acta Anaesthesiol Belg 1986;37:127-36.

20. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62:310-24.

21. de Jong RH, Bonin JD. Deaths from local anesthetic-induced convulsions in mice. Anesth Analg 1980;59:401-5.

22. Hardin RL, Yagiela JA, Bilger PAL, Hunt LM. Influence of epinephrine on intravascular lidocaine toxicity. J Dent Re: 1981;60(A):463.

23. Chadwick HS. Toxicity and resuscitation in lidocaine or bupivacaine-infused cats. Anesthesiology 1985;63:385-90.

24. Liu PL, Feldman HS, Giasi R, Patterson MK, Covino BG Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine in awake dogs following rapid intravenous administration. Anesth Analg 1983;62:375-9.

25. Mallampati SR, Liu PL, Knapp RM. Convulsions and ventricular tachycardia from bupivacaine with epinephrine. Anesth Analg 1984;63:856-9.

26. Yagiela JA. Intravascular lidocaine toxicity: influence of epinephrine and route of administration. Anesth Prog 1985;32:57-61.

27. Yagiela JA, Madsen WC. Mechanism of enhancement of lidocaine toxicity by epinephrine. J Dent Res 1982;61:275.

The Screening of Propofol in MHS Swine

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This study investigated the use of propofol in swine genetically susceptible to malignant hyperthermia (MH). Thirteen animals were exposed to 2% halothane in inspired air, a propofol infusion of 12 mg·kg^{-1}·hr^{-1} for up to 45 min, or a combination of both. When MH was triggered the animals were treated with dantrolene. Mean onset time of malignant hyperthermia on exposure to halothane alone was 7.2 min $\pm$ *3.0 min and onset with propofol and halothane was 5.0* $\pm$ *2.5 min. In no instance did propofol alone trigger the syndrome nor was there a statistical difference (P < 0.05) in onset time when the drug was used in conjunction with halothane. On the basis of these results, we conclude that propofol is almost certainly safe for use in humans who are susceptible to MH.*

Key Words: ANESTHETICS, INTRAVENOUS—propofol. HYPERTHERMIA—malignant.

The precipitation of malignant hyperthermia (MH) in genetically susceptible (MHS) individuals by exposure to certain anesthetic drugs and adjuvants renders essential the screening for such property of all newly developed anesthetics (1). We report here on the screening in MHS swine of the newly introduced intravenous anesthetic propofol (2) to determine its potential for eliciting or preventing or attenuating halothane induction of MH.

Methods

Specially bred MHS Landrace swine (20–65 kg weight), initially identified by their positive MH response to a brief "barnyard" mask exposure to halothane (1), were selected for this study. Under thiopental/N$_2$O/O$_2$ anesthesia with appropriate monitoring, the animals were exposed to propofol and halothane in the following protocol in random order and evidence of the onset of MH was sought: 1) To halothane alone; 2) To propofol alone for 45 min; 3) To propofol for 45 min followed by halothane alone; and 4) To both propofol and halothane simulta-

neously, with propofol given ten min before exposure to halothane.

In each of the above circumstances except the second, halothane was to be continued until triggering of MH occurred or, failing this, for 60 minutes. Exposures were separated by 72 hours to ensure adequate recovery of the animals. Individual animals were submitted to procedures 1, 2 and 3 or 1, 2 and 4.

All animals were anesthetized with 4 mg/Kg i.v. thiopental (ear vein on first occasion, jugular cannula subsequently), intubated and mechanically ventilated with N$_2$O/O$_2$ (FiO$_2$ = 0.4) using a non-rebreathing circuit. Minute volume was regulated to maintain Paco$_2$ in the range 40–45 mm Hg. Pao$_2$ ranged from 180–220 mm Hg while the mean pH during control periods was 7.412 (+/−0.05).

The internal carotid artery and jugular vein were cannulated by cut-down in the neck providing access to arterial blood samples for serial measurements of blood gas tensions and acid/base status (Radiometer), arterial and venous pressure monitoring (Hellige), and administration of fluids and drugs. The ECG was monitored using skin electrodes, the temperature by means of a thermistor probe (ELAB) inserted deep into the thigh muscle mass, and F$_E$CO$_2$ by sampling of gases at the proximal tracheal tube mount by capnography (Morgan).

Following anesthesia and the establishment of a hemodynamic steady state, propofol was administered as a continuous intravenous infusion of 12

Table 1. MH Onset Times

Drug Exposure	MH Onset Times (in minutes)		Number of Animals
Protocol	Mean	SD	
Halothane	7.2	± 3.0	13
Propofol	No MH	—	13
Propofol→Halothane	8.7	± 4.4	7
Propofol + Halothane	5.0	± 2.5	6

$mg \cdot kg^{-1} \cdot hr^{-1}$ (the upper limit of the recommended human dose) (2). Halothane 2% in inhaled air was administered into the fresh gas flow by means of a Fluotec Mark 2 vaporizer.

The onset of MH (1) was manifested by all of the following: 1. Muscle fasiculation proceeding to rigor, seen in the supine pig most clearly by extension of the hind legs; 2. A gross increase (>2%) in F_ECO_2 (a manifestation of the development of metabolic and respiratory acidosis); 3. Tachycardia and an increase in blood pressure (manifestations of the systemic release of cathecolamines); 4. A progressive fulminant increase in body temperature of 1°C/5–10 min, terminating halothane exposure after a rise above 40°C.

In these experiments the commencement of a progressive extension of the hind legs was recorded as the time of onset of MH. Increases in F_ECO_2 and core temperature were measured thereafter as confirmatory evidence of the onset of the syndrome. Further evidence of the initiation of the syndrome was sought in the gross increase in serum creatine phosphokinase (CPK) levels 24 hours later.

When triggered, MH was allowed to continue until an increase in core temperature at 1–2°C had occurred. The animals were then treated, following discontinuance of halothane, by the administration of dantrolene, 4.2% sodium bicarbonate, and hyperventilation with 100% oxygen.

The statistical significance of differences in mean times to onset of MH was tested by Student's t test ($P < 0.05$).

Results

Results are summarized in Table 1. Exposure to halothane triggered MH in all animals. No animal developed MH when exposed to propofol alone. Administration of propofol failed to prevent or attenuate halothane triggering of the syndrome (protocols 3 and 4), there being no statistically significant differ-

ence in times of onset. On each occasion that MH was clinically evident its presence was subsequently confirmed by many-fold increases in serum CPK levels sampled at 24 hours.

Discussion

Despite their heterogeneity, no intravenous anesthetic agent has been shown to trigger MH in susceptible patients (1). However, an effect on halothane provocation of MH has been attributed to althesin, thiopental and etomidate. Althesia has been reported to block it (3), thiopental to attenuate (4) and etomidate to enhance the time of onset of MH (5).

Our observations show that propofol, does not trigger MH in MHS swine nor has it any modifying effect on halothane provocation of the syndrome. These data indicate that propofol may be safely used as an anesthetic for individuals known to be susceptible to MH.

Study of propofol in MHS swine for its effects alone and on halothane induction of MH as described indicates that propofol neither elicits nor modifies halothane induction of malignant hyperthermia in MHS swine. We conclude that propofol may be safely used as an anesthetic in patients known to be susceptible to MH.

References

1. Harrison GG, Porcine MH. In: Britt BA, ed. 'Malignant Hyperthermia.' Boston: Martinus Nijhoff Publishing, 1987:103–36.

2. Symposium: Propofol (Diprivan). A new intravenous anaesthetic. Postgrad Med J 1985;61:Suppl. 3:1–169.

3. Harrison GG. Alfathesin and malignant hyperpyrexia. Br J Anaesth 1973;45:1019–21.

4. Hall LW, Trimm MN, Woolf N. Further studies of malignant hyperthermia. Br Med J 1972;2:145–84.

5. Suresh MS, Nelson TE. Malignant hyperthermia: is etomidate safe? Anesth Analg 1985;64:420–4.

Hemodynamic Dose-Responses to Halothane and Isoflurane Are Different in Swine with and without Critical Coronary Artery Stenosis

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GILBERT M, MORI M, MYHRE ESP. Halothane and isoflurane have different dose-responses hemodynamic in swine with and without critical coronary artery stenosis. Anesth Analg 1989;68:752–8.

This study examined global hemodynamic responses to increasing concentrations of halothane and isoflurane in pigs with an acute critical coronary stenosis (CCS) on the left anterior descending coronary artery (LAD). The CCS was caused by graded inflation of an hydraulic occluder to the point where no hyperemic response was observed following a 10 sec. total LAD-occlusion. A minute, piezoelectric epicardial Doppler probe applied without dissection was used to monitor the stenosis. Previously reported minimum alveolar concentrations (MAC) were used as endtidal concentrations ([Et]). The [Et] was increased stepwise until each animal died. Recordings obtained in this study were compared to recordings obtained during similar stepwise increments of these anesthetics in pig preparations without CCS. Isoflurane had a significantly less depressant effect on global hemodynamics compared to halothane and caused death at higher MAC than halothane in either case. A critical LAD-stenosis caused no major changes in the general dose-response pattern of isoflurane but further aggravated the depression of cardiac output and stroke volume induced by increasing concentrations of halothane.

Key Words: HEART—coronary artery occlusion. ANESTHETICS, VOLATILE—halothane, isoflurane. ANESTHESIA, CARDIOVASCULAR.

Halothane causes dose-dependent depression of myocardial performance (1,2). In hearts supplied by a 'critically' narrowed coronary artery, ventricular function responds in a similar way to halothane (3). Studies of regional myocardial fibre length, ventricular wall thickness and myocardial metabolism during halothane anesthesia have shown aggravated and eventual permanent dysfunction in the areas of ischemic myocardium (3–6). Halothane given to patients with coronary artery disease has been shown not to influence myocardial oxygenation (7–9).

Isoflurane causes less myocardial depression and thus affects ventricular function less than halothane (10). In humans with ischemic heart disease, however, isoflurane with nitrous oxide or with thiopentone causes coronary vasodilation and myocardial

ischemia explained by a mechanism of coronary steal (11,12). Animal studies with isoflurane and coronary stenosis have demonstrated the opposite, i.e. preserved regional myocardial function and endocardial blood flow with conflicting evidence of coronary steal (13,14). A "critical coronary stenosis" has been defined as a stenosis that prevents reactive and active hyperemia of total coronary blood flow without affecting resting blood flow (15,16). The vascular bed distal to such a degree of narrowing is maximally dilated and subendocardial vasodilator reserve exhausted (17).

We hypothesized that a critical coronary stenosis would affect coronary vascular reserve in such a way as to amplify inherent differences between halothane and isoflurane. Epicardial collateralization is species dependent. In this study, swine were used to minimize the influence of coronary collaterals. Experiments were performed in pigs with similar degree coronary stenosis during exposure to equivalent step increments in [Et] of halothane or isoflurane until each animal died in order to examine how different concentrations of halothane and isoflurane influence global myocardial function.

Materials and Methods

Instrumentation

Fourteen young male mongrel pigs (Sus scrofa) weighing 26–37 kg fasted 12 hours before the experiments. Anesthesia was induced without premedication with one of either inhalation agent in oxygen via animal anesthesia mask. Muscle relaxant and maintenance fluids were given in a catheter placed in an ear vein. Tracheal intubation was performed via the tracheotomy following muscle paralysis. Animals were kept normothermic with external heating lamps and warming blankets and ventilated with a volume-controlled ventilator to get a pCO_2 of 35–45 mm Hg. Aortic pressure (AP) was transduced via the right common carotid artery. Pulmonary arterial pressure (PAP), pulmonary artery wedge pressure (PCWP), right atrial pressure (RAP), and thermodilution-determined cardiac output (CO) were measured via a 7F thermodilution catheter inserted via the internal jugular or the femoral vein. AP, PAP, and ECG were continuously displayed and recorded. Coronary perfusion pressure (CPP) was calculated as diastolic aortic pressure minus PCWP. CO was measured in triplicate at each recording using injections of iced 5% dextrose. Arterial blood gas tension and pH were measured frequently during each experiment. End-tidal concentrations of isoflurane ($[Et]_{iso}$) and halothane ($[Et]_{halo}$) were measured in gas samples with a calibrated mass spectrometer (Perkin Elmer) in samples continuously aspirated from the endotracheal tube. Surgery was performed at about 1 MAC $[Et]_{agent}$ with the anesthetist administering more or less agent according to clinical signs of stress in the animal. The pericardium was exposed through a median sternotomy and the heart was suspended in a pericardial cradle. A small glycerine-filled hydraulic occluder was placed proximally on the left anterior descending coronary artery (LAD) after a circumferential dissection. An oiled 3-0 silk ligature was placed loosely around the vessel next to the occluder and rigged via a tube with inner diameter of 0.5 mm. Thus rapid on/off occlusion of the vessel could be created to produce coronary reactive hyperemia. LAD coronary blood flow velocity was measured with a 20 mHz piezoelectric ultrasonic pulsed Doppler probe (18) placed in a lightweight (<0.5 g), 5 mm diameter silicone suction cup (19). The probe was attached on the LAD with vacuum just distal to the occluder and the snare. The position was adjusted to obtain a maximum phasic signal. The signal was meaned via a pulsed Doppler flowmeter. The presence or absence of reactive hyperemia was determined by observing changes in the distal flow velocity following 10-sec arterial occlusions. By gradually expanding the occluder with glycerine via a micrometer we established the critical coronary stenosis (CCS) at the point where the LAD occlusion caused no reactive hyperemia upon release. This has been considered to occur when a stenosis is such that distal coronary vasculature is maximally dilated (15). The critical stenosis was made during MAC [Et] of either anesthetic prior to recordings. This stenosis (i.e., volume of glycerine in the occluder) was not changed during the experiment. Control animals had similar instrumentation without CCS creation. These animals were tested with brief (15 sec) LAD-occlusions at each MAC level to quantitate coronary reserve (20).

Drugs

We used 1.45% $[Et]_{iso}$ and 1.25% $[Et]_{halo}$ as MAC for pigs (21,22). No premedicants or other drugs were given during the study, except succinylcholine as needed to maintain muscle paralysis.

Experimental Protocol

Since only one anesthetic was tested in each experiment, each pig served as its own control with control levels defined as 0.5 MAC of either agent. Fourteen pigs were randomly assigned to two groups, 7 to be anesthesized with isoflurane (ISO STENOSIS), 7 with halothane (HALO STENOSIS) after being prepared as described above with a critical LAD stenosis. To assess effects of the anesthetic agents in presence of a CCS, we used data from animals exposed to identical surgery and isoflurane or halothane concentrations but without CCS. These 14 control animals were randomly assigned to anesthesia with isoflurane (ISO CONTROL, N = 7) or halothane (HALO CONTROL, N = 7) using similar, equipotent MAC-increments (20).

Recordings were done at steady-state [Et] of 0.5, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 MAC of each anesthetic until the animal died. At least 15 minutes was allowed for blood-brain equilibration at each concentration prior to recordings.

Statistical Analysis

Each pig served as its own control with reference level being 0.5 MAC. Values were tested for normality and presented as mean ± SEM. Analysis of variance for repeated measures (ANOVA) was per-

Table 1. Endtidal Isoflurane or Halothane Concentrations (ET), Carbon Dioxide Tension, and pH in Pigs With or Without a Critical Stenosis on the Left Anterior Descending Coronary Artery. Values are Mean ± SEM

	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3 MAC	ANOVA
N									
ISO contr.	7	7	7	7	7	7	7	4	
ISO sten.	7	7	7	7	7	7	7	5	
HALO contr.	7	7	7	6	3	–	–	–	
HALO sten.	7	7	7	5	2	–	–	–	
Et %									
ISO contr.	.69 ± .02	1.45 ± .01	1.84 ± .02	2.16 ± .02	2.54 ± .01	2.88 ± .01	3.6 ± .01	4.26 ± .03	
ISO sten.	.72 ± .01	1.49 ± .03	1.80 ± .01	2.21 ± .02	2.55 ± .02	2.91 ± .03	3.68 ± .04	4.34 ± .01	
HALO contr.	.62 ± .01	1.26 ± .01	1.57 ± .01	1.86 ± .01	2.21 ± .02	–	–	–	
HALO sten.	.63 ± .01	1.25 ± .01	1.56 ± .01	1.89 ± .01	2.2 ± .02	–	–	–	
PaCO$_2$ (mm Hg)									
ISO contr.	38 ± 1	38 ± 1	38 ± 1	36 ± 1	38 ± 1	39 ± 1	38 ± 2	38 ± 3	
ISO sten.	38 ± 1	36 ± 1	36 ± 1	35 ± 1	37 ± 1	38 ± 2	38 ± 4	36 ± 1	
HALO contr.	38 ± 3	37 ± 2	39 ± 2	34 ± 2	–	–	–	–	NS
HALO sten.	39 ± 2	38 ± 2	32 ± 3	40 ± 1	–	–	–	–	
pH									
ISO contr.	7.49 ± .01	7.51 ± .01	7.52 ± .02	7.52 ± .01	7.49 ± .01	7.47 ± .02	7.49 ± .02	7.41 ± .02	
ISO sten.	7.50 ± .01	7.50 ± .01	7.51 ± .02	7.53 ± .01	7.50 ± .01	7.46 ± .02	7.48 ± .02	7.48 ± .02	
HALO contr.	7.52 ± .03	7.54 ± .02	7.45 ± .02*	7.52 ± .04	–	–	–	–	$
HALO sten.	7.45 ± .02	7.46 ± .01ᵃ	7.45 ± .02	7.49 ± .03	–	–	–		

Legends: MAC, minimum alveolar concentration; ISO contr., isoflurane group without critical coronary stenosis (CCS) on LAD; ISO sten., isoflurane group with LAD-CCS; HALO contr., halothane group without LAD-CCS; HALO sten., halothane group with LAD-CCS; N, number of animals alive following 15-min stabilization; Et %, endtidal concentration of anesthetic; PaCO$_2$, arterial carbon dioxide tension. Statistics: ANOVA: NS, not significant; $, significant interaction between group and MAC; *, $P < 0.05$ vs control (0.5 MAC); a, $P < 0.05$ vs HALO control.

formed for each response variable in order to test effects of CCS, the anesthetic agents and dose. Accordingly, independent variables were anesthetic concentration (MAC) and the 4 groups (with/without CCS, isoflurane, or halothane). If the F-value of the group by MAC interaction was significant; (i.e., the rate of change in the dependent variable was significantly different between the groups), the dose effects were evaluated for each group and the group effect for each concentration level with t-tests. If interaction was insignificant, the main effects of dose (MAC effect) and group belonging (group effect) were tested as contrasts. Due to the earlier deaths observed in the halothane groups and the small number of remaining animals, such comparisons were only possible up to 1.5 MAC for all 4 groups. In the isoflurane group, analysis of variance and comparisons within and between isoflurane groups were performed separately up to 3 MAC. To test differences in the slopes of the dose-response patterns in each group, linear regressions between the response variable and individual [Et]$_{agent}$ were performed for each experiment. The a-value of the calculated formula $y = ax + b$ of each experiment was compared between the groups with and without stenosis using two-tailed, unpaired t-tests.

Follow-up tests were performed with Bonferroni adjustment to protect the overall p-value for a general significant level of 0.05. All statistical analyses were performed using Statistical Analysis System (SAS 82.4) or a StatPac computer program.

Results

Table 1 shows the number of animals alive after a 15-min stabilizing period at each MAC-level of isoflurane or halothane. [Et] of isoflurane and halothane, arterial carbon dioxide tension and pH are also shown in Table 1. Hemodynamic variables are presented in Table 2. We found no significant difference between groups at 0.5 MAC [Et]. Both anesthetics caused dose-dependent, significant decreases in aortic pressure, cardiac output, and stroke volume but the decrease became apparent at lower concentrations of halothane than isoflurane. MAP was significantly less at 1.0 MAC than at 0.5 MAC with both agents, but MAP decreased more with halothane than isoflurane at all levels above 0.5 MAC. CO and SV decreased with increasing concentrations of halothane from 1.0 MAC. In the isoflurane groups, the reduction was significant compared to 0.5 MAC at

Table 2. Hemodynamic Effects of Increasing Endtidal Isoflurane and Halothane Concentrations in Pigs With or Without a Critical Stenosis on the Left Anterior Descending Coronary Artery

	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3 MAC	ANOVA
HR (beats·min⁻¹)									
ISO contr.	108 ± 11	100 ± 7	94 ± 6	87 ± 2*	86 ± 4*	93 ± 5	95 ± 6	105 ± 12	
ISO sten.	98 ± 8	92 ± 6	92 ± 5	90 ± 5	91 ± 6*	94 ± 7	82 ± 14*	92 ± 9	
HALO contr.	100 ± 7	86 ± 7	98 ± 8	96 ± 8	(113 ± 8)	–	–	–	$
HALO sten.	100 ± 7	102 ± 6	106 ± 7	108 ± 6	(118 ± 18)	–	–	–	
MAP (mm Hg)									
ISO contr.	82 ± 6	65 ± 3*	62 ± 2*	56 ± 2*	54 ± 2*	50 ± 2*	36 ± 6*	28 ± 9*	
ISO sten.	75 ± 5	56 ± 4*	53 ± 5*	53 ± 3*	51 ± 4*	48 ± 4*	38 ± 7*	34 ± 4*	
HALO contr.	67 ± 2	41 ± 3*	37 ± 2*	31 ± 3*	(25 ± 8)	–	–	–	$
HALO sten.	66 ± 5	49 ± 3*	47 ± 4*	38 ± 5*	(53 ± 6)	–	–	–	
CARDIAC OUTPUT (L·min⁻¹)									
ISO contr.	4.07 ± .48	3.58 ± .57	3.05 ± .34*	2.74 ± .36*	2.55 ± .35*	2.36 ± .33*	2.07 ± .4*	1.96 ± .67*	
ISO sten.	3.37 ± .19	2.69 ± .09	2.59 ± .15*	2.36 ± .12*	2.43 ± .11*	2.29 ± .17*	1.72 ± .21*	1.61 ± .11*	
HALO contr.	4.84 ± .58	2.88 ± .45*	2.67 ± .41*	1.74 ± .40*	(1.7 ± .5)	–	–	–	$
HALO sten.	3.38 ± .3	2.31 ± .2*	2.26 ± .26*	1.71 ± .37*	(2.27 ± .18)	–	–	–	
STROKE VOLUME (ml·beat⁻¹)									
ISO contr.	38.6 ± 4.7	36.5 ± 5.8	33.1 ± 4.0	31.4 ± 4*	30.2 ± 4.2*	25.9 ± 3.8*	21.8 ± 4*	18.3 ± 6*	
ISO sten.	35 ± 1.7	29.8 ± 1.7	28.3 ± 1.7	26.8 ± 2.1*	27.3 ± 1.9*	25 ± 2.6*	18.3 ± 2.5*	14.5 ± 4.9*	
HALO contr.	47.9 ± 4.3	33.2 ± 5.3*	27.4 ± 4*	18.2 ± 3.9*	(15.4 ± 4.6)	–	–	–	$
HALO sten.	35.1 ± 4	23.7 ± 3.3*	22.8 ± 4.1*	17.1 ± 4.9*	(20 ± 4.5)	–	–	–	
MPAP (mm Hg)									
ISO contr.	14 ± 1	17 ± 2	18 ± 3	15 ± 2	14 ± 3	13 ± 3	13 ± 2	13 ± 2	
ISO sten.	10 ± 2	11 ± 3	11 ± 4	10 ± 1	11 ± 1	11 ± 2	13 ± 5	14 ± 3 ⌋	
HALO contr.	21 ± 1	19 ± 2	18 ± 2	19 ± 1	(21 ± 4)	–	–	–	NS
HALO sten.	20 ± 2	19 ± 4	16 ± 3	28 ± 4	–	–	–	–	
PCWP (mm Hg)									
ISO contr.	10 ± 1	10 ± 1	11 ± 1	9 ± 2	8 ± 3	9 ± 3	8 ± 3	16 ± 1 ⌉	&
ISO sten.	4 ± 1	4 ± 1	7 ± 4	4 ± 1	5 ± 1	4 ± 2	6 ± 2	8 ± 2 ⌋	$P < .05$
HALO contr.	12 ± 1	10 ± 2	12 ± 1	12 ± 1	(14 ± 3)	–	–	–	
HALO sten.	6 ± 1	6 ± 1	7 ± 1	7 ± 2	(9 ± 1)	–	–	–	$P < .05$
CPP (mm Hg)									
ISO contr.	56 ± 7	43 ± 3ᴵ	39 ± 3ᴵ	35 ± 3ᴵ	32 ± 5	28 ± 4	19 ± 2	13 ± 3	&
ISO sten.	59 ± 6	42 ± 5	39 ± 4	40 ± 4	36 ± 4	32 ± 5	28 ± 6	19 ± 4 ⌉	$P < .05$
HALO contr.	42 ± 2	19 ± 3	15 ± 2	11 ± 2	(2 ± 4)	–	–	– ⌋	$P < .05$
HALO sten.	53 ± 5	36 ± 3	34 ± 3	24 ± 5	(27 ± 1)	–	–	–	
SVR (dynes·sec⁻¹·cm⁻⁵)									
ISO contr.	1698 ± 211	1656 ± 225	1745 ± 202	1804 ± 211	1906 ± 279	1899 ± 263	1422 ± 115	1209 ± 368	
ISO sten.	1813 ± 181	1680 ± 179	1661 ± 202	1819 ± 176	1665 ± 107	1697 ± 129	1926 ± 167	1680 ± 171	
HALO contr.	1297 ± 288	1671 ± 644	1321 ± 281	1584 ± 341	(1288 ± 479)	–	–	–	$
HALO sten.	1595 ± 104	1743 ± 156	1690 ± 96	2029 ± 208	(1840 ± 52)	–	–	–	
PVR (dynes·sec⁻¹·cm⁻⁵)									
ISO contr.	311 ± 48	462 ± 114	531 ± 110	496 ± 110	490 ± 153	458 ± 128	563 ± 172*	975 ± 541*	
ISO sten.	239 ± 56	322 ± 91	377 ± 165	339 ± 58	365 ± 55	367 ± 58	629 ± 238*	685 ± 170*	
HALO contr.	292 ± 64	573 ± 25	496 ± 126*	932 ± 203*	(900 ± 333)	–	–	–	$
HALO sten.	349 ± 35	463 ± 81	407 ± 71	621 ± 146	(766 ± 82)	–	–	–	
RAP (mm Hg)									
ISO contr.	NA								
ISO sten.	3 ± 2	5 ± 2	5 ± 1	5 ± 1	7 ± 2	8 ± 3	8 ± 3		
HALO contr.	NA							⌉	$P < .05$
HALO sten.	6 ± 1	8 ± 1ᵃ	10 ± 2ᵃ	–	–	–	–	⌋	

Legends: See Table 1. HR, Heart rates; MAP, mean aortic pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary artery wedge pressure; CPP, coronary perfusion pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; RAP, right atrial pressure. ANOVA: NS, not significant; NA, not analysed; $, significant interaction between group and MAC; &, significant contrast between groups; l, significant contrasts between MAC-levels vs 0.5 MAC. Follow-up tests: *, $P < 0.05$ vs control (0.5 MAC); a, $P < 0.05$ vs ISO sten. Values in ( ) are not included in ANOVA with follow-up tests.

1.25 MAC for CO and from 1.5 MAC for SV. Heart rates (HR) decreased with increasing isoflurane concentrations at 1.5 and 1.75 MAC. Systemic vascular resistance (SVR) was however not affected by either agent, level of concentration or presence, or absence of stenosis. Calculated coronary perfusion pressure (CPP) was overall lower at 1, 1.25, and 1.5 MAC with either agent when compared to 0.5 MAC values. In the halothane groups, CPP was higher in animals with CCS. PCWP was lower with than without CCS during both anesthetic agents. Right atrial pressure (RAP) was similar at 0.5 MAC in the two groups with CCS. It remained unchanged in the isoflurane group with CCS. It increased significantly, however, with increasing concentrations of halothane in CCS animals. Pulmonary vascular resistance (PVR) increased in nonstenotic animals anesthesized with halothane at 1.25 and 1.5 MAC and in isoflurane animals at 2.5 and 3 MAC. Mean pulmonary artery pressure was unaffected both by absence or presence of coronary stenosis and by anesthetic agent or concentration.

Table 3 shows the results of analyzing the linear regression slopes for each individual experiment. It appears that with isoflurane, the presence of a CCS-LAD caused no shift in the slope of dose-response pattern for HR, MAP, CPP, MPAP, PCWP, CO, SV, and SVR. Contrary, in the halothane group, presence of a CCS-LAD affected the slopes of the linear regression for HR, CO and SV. With CCS-LAD, HR were higher and CO and SV lower than without CCS. Also, animals given halothane were different from those given isoflurane in comparing the regression equations from experiments with CCS-LAD in that they showed significantly different slopes for HR, CO and SV.

Discussion

We consider this porcine model of coronary artery stenosis to be relevant for studying the dose-response effects of inhalation anesthetics during conditions of compromised myocardial blood flow. Unlike canine myocardium, in the porcine myocardium few subendocardial and epicardial collaterals exists in the non-diseased heart and they are considered to be similar in extent and location to those found in healthy human hearts (23,24). A critical coronary stenosis as defined will reduce vessel diameter by 88–93% (10) but resting coronary flow is reduced about 9–19% (16,17). Patients with coronary artery disease with severe coronary stenoses (vessel reduced 75–98% in diameter), generally do not have collaterals that can be demonstrated angiographically (25). Therefore,

Table 3. Comparison of the Coefficients from Linear Regressions of Individual Endtidal Anesthetic Concentrations and Response Variables

Response variable	Isoflurane with vs without LAD-CCS	Halothane with vs without LAD-CCS	Halothane vs isoflurane with LAD-CCS
HR	NS	$P = 0.0004$	0.016
MAP	NS	NS	NS
MPAP	NS	NS	NS
CPP	NS	NS	NS
PCWP	NS	NS	NS
CO	NS	$P = 0.015$	$P = 0.0009$
SV	NS	$P = 0.014$	$P = 0.0044$
SVR	NS	NS	NS

NS, not significant. P-values are from unpaired, two-tailed t-tests.

the exposure to inhalation anesthetics and surgery in this pig model may reflect the conditions during ischemic heart disease in man with critically stenosed but not totally occluded coronary arteries. A pig preparation with an acute critical stenosis of the LAD is a useful, reproducible model of ischemia although it may not mimic chronic, occlusive multivessel coronary disease in man. We did not interfere with cardiac mechanics except for the minimal LAD dissection. The invasive variables recorded are those usually available during human surgery.

The major finding of this study is that a single critical LAD coronary stenosis (LAD-CCS) does not change the hemodynamic dose-response effects of isoflurane whereas it seems to further impair global myocardial function when using halothane.

Our hemodynamic findings thus confirm the observation that halothane-induced depression of global myocardial function differs from that of isoflurane (26). Our data differ somewhat from the results of Lowenstein et al. who found a well-preserved cardiovascular function in dogs with a critical LAD-stenosis exposed to increasing halothane concentrations (3). However, regional myocardial dysfunction in the LAD-territory was demonstrated by measuring myocardial fibre length although systemic hemodynamics were considered appropriate for the anesthetic concentration and there were no ECG changes. They found significant difference in segment length and contraction patterns between the LAD segment and normal myocardium starting at 0.5% inspired halothane. It was concluded that the absence of global impairment of LV function does not preclude regional ischemic dysfunction in areas supplied by critically narrowed coronary arteries (3). We found that with halothane, a CCS-LAD did reduce CO and SV and increased HR. One explanation may be that, although we do not provide data without anesthesia, the observed differences in CO and SV

between pigs given halothane with and without stenosis might be reflecting more baseline differences at 0.5 MAC halothane than the LAD-CCS. Pigs with LAD-CCS had numerically (but not statistically) reduced CO and SV already at 0.5 MAC halothane. Another possible explanation is the different animal model we used. Since canine myocardia have extensive collaterals, collateral flow might have compensated the reduced and pressure-dependent blood flow distal to the stenosed LAD so that only local signs of ischemic dysfunction were detectable in the study by Lowenstein et al. In the pig, collateral inflow to the compromized territory distal to the LAD-CCS is less likely. Thus, although we did not measure regional function, we propose that the LAD-CCS caused regional dysfunction that could not be alleviated by collateral inflow and thus caused reductions in global myocardial function in our pig model.

A critical coronary artery stenosis eliminates autoregulation in the subendocardium while the subepicardial vasodilator reserve remains intact (17). During increased myocardial oxygen demand, further dilatation of epicardial coronary arteries may produce increased blood flow to the epicardium through a redistribution of myocardial blood flow with a potentially deleterious transmural steal, and decreased subendocardial perfusion may be created (27). Direct pharmacologic dilation of coronary vessels could cause the same decrease in coronary vasodilator reserve. We have previously shown halothane to cause a significant reduction in coronary reserve in pigs at 1.25 and 1.5 MAC halothane (20). This may explain in part the regional dysfunction in areas supplied by a critically narrowed LAD by a mechanism of transmural steal in spite of constant or even reduced oxygen demand. Since perfusion distal to the stenosis is pressure dependent due to the restricted flow, dose-dependent reduction in coronary perfusion pressure would also be augmented by simultaneous epicardial vasodilation. With isoflurane in equipotent concentrations to halothane, the coronary vasodilator reserve is unchanged (20). It is therefore likely that perfusion distal to the stenosis in the halothane group was more pressure dependent than in the isoflurane group since halothane per se causes a reduced coronary vascular reserve. We found higher coronary perfusion pressure with isoflurane than with halothane in animals with critically narrowed LAD, and we propose that this may explain why halothane caused death at significantly lower concentrations than isoflurane (28). CCS-LAD animals anesthetized with halothane had higher CPP than nonconstricted exposed to halothane but lower than the isoflurane group with CCS-LAD. Thus, in spite of significantly higher CPP in halothane ani-

mals with LAD-stenosis, cardiac function did not improve nor survive to higher MAC of halothane.

One may argue that the definition of a critical coronary stenosis is not good enough. A stenosis sufficient to exhaust dilator reserve without changing blood flow at rest is reached at a reduction of between 75–90% of vessel diameter (15,16). Various reports indicate the reduction in resting coronary flow at this degree of stenosis which varies from very little to 19% (15,5,16). Such decrements in coronary blood flow are too small to cause myocardial ischemia which in other animal studies have been shown to appear with coronary flow reductions of approximately 40–50% (5,29,30). However, a CCS would deplete coronary reserve and make myocardial perfusion dependent on changes in perfusion pressure and redistribution of transmural flow caused by the volatile anesthetics. Further, a critical coronary stenosis would be more similar to the situation where the coronary artery diameter was reduced by disease but *not* occluded. A significant coronary stenosis in man describes a vessel with a diameter reduction of 75–90% (15,16). Patients with coronary heart disease and critical stenosis of coronary vessels (75–98% reduced vessel diameter) generally do not have collaterals that may be demonstrated angiographically (25). The presented pig model with poorly collateralized myocardia and a CCS, might therefore be relevant to test hemodynamic effects of volatile anesthetics.

In summary, graded increments of isoflurane in pigs with a single, critical LAD stenosis did not cause larger impairment of global ventricular function than in animals without coronary stenosis. With halothane during similar conditions, CO, and SV decreased while HR and RAP increased indicating deteriorating cardiac function. Although the compromised myocardial territory with a single, critical LAD stenosis may be too small to cause significant global myocardial ischemic dysfunction in well-collateralized myocardium, halothane was clearly more depressant on myocardial function than isoflurane in this noncollateralized pig model.

References

1. Vatner SF, Ty Smith N. Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. Circ Res 1974;34:155–67.

2. Merin RG, Kumazawa T, Luka NL. Myocardial function and metabolism in the conscious dog and during halothane anesthesia. Anesthesiology 1976;44:402–14.

3. Lowenstein E, Foex P, Francis CM, Davies WL, Yusuf S, Ryder WA. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in dogs. Anesthesiology 1981;55:349–59.

4. Verrier ED, Edelist G, Consigny PM, Robinson S, Hoffman JIE. Greater coronary vascular reserve in dogs anesthesized with halothane. Anesthesiology 1980;53:445–59.

5. Hickey RF, Verrier ED, Baer RW, Vlahakes GJ, Fein G, Hoffman JIE. A canine model of acute coronary artery stenosis: Effects of deliberate hypotension. Anesthesiology 1983;55:226–36.

6. Ramsay JG, Arvieux CC, Foex P, Philbin DM, Jeavons P, Ryder WA, Jones LA. Regional and global function in the dog when nitrous oxide is added to halothane in the presence of critical coronary artery constriction. Anesth Analg 1986;65:431–6.

7. Moffitt EA, Sethna DH, Bussell JA, Raymond M, Matloff JM, Gray RJ. Myocardial metabolism and hemodynamic response to halothane and or morphine anesthesia for coronary artery surgery. Anesth Analg 1982;61:979–85.

8. Sonntag H, Merin RG, Donath U, Radke J, Schenk HD. Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. Anesthesiology 1979;51:204–10.

9. Reiz S, Balfors E, Gustavsson B. Effects of halothane on coronary hemodynamics and myocardial metabolism in patients with ischaemic heart disease and heart failure. Acta Anaesthesiol Scand 1982;26:133–8.

10. Eger EI, II. Isoflurane: A review. Anesthesiology 1981;55:561–76.

11. Reiz S, Bälfors E, Sorenson MB, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.

12. Moffitt EA, Barker RA, Glenn JJ, Imrie DD, DelCampo C, Landymore RW, Kinley CE, Murphy DA. Myocardial metabolism and hemodynamic response with isoflurane anesthesia for coronary artery surgery. Anesth Analg 1986;65:53–61.

13. Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF. Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow. Their capacity to induce coronary steal. Anesthesiology 1987;67:665–75.

14. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.

15. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Am J Cardiol 1973;33:87–94.

16. Elzinga WE, Skinner DB. Hemodynamic characteristics of critical stenosis in canine coronary arteries. J Thorac Cardiovasc Surg 1975;69:217–24.

17. Gallagher KP, Osakada G, Matsuzaki M, Scott Kemper W, Ross J. Myocardial blood flow and function with critical coronary stenosis in exercising dogs. Am J Physiol 243 (Heart Circ Physiol 12) 1982;H698–H707.

18. Hartley CJ, Cole JS. An ultrasonic pulsed Doppler system for measuring blood flow in small vessels. J Appl Physiol 1974;37: 626–31.

19. Marcus M, Wright C, Doty D, Eastham C, Laughlin D, Krumm P, Fastenow C, Brody M. Measurements of coronary velocity and reactive hyperemia in coronary circulation in humans. Circ Res 1981;49:877–91.

20. Gilbert M, Roberts SL, Mori M, Blomberg R, Tinker JH. Comparative coronary vascular reactivity and hemodynamics during halothane and isoflurane anesthesia in swine. Anesthesiology 1988;68:243–53.

21. Eisele PH, Talken L, Eisele JH. Potency of isoflurane and nitrous oxide in conventional swine. Lab Anim Sci 1985;35: 76–8.

22. Weiskopf RB, Bogetz MS. Minimum alveolar concentrations (MAC) of halothane and nitrous oxide in swine. Anesth Analg 1984;63:529–32.

23. Jonsson L. A microangiographic study of the normal intramural vascular pattern of the porcine heart. J Am Vet Radiol Soc 1975;16:13–7.

24. White FC, Roth DM, Bloor CM. The pig as a model for myocardial ischemia and exercise. Lab Anim Sci 1986;36:351–6.

25. Elayda M, Mathur VS, Hall RJ, Massumi GA, Garcia E, de Castro CM. Collateral circulation in coronary artery disease. Am J Cardiol 1985;55:58–60.

26. Jones RM. Clinical comparison of inhalation anaesthetic agents. Br J Anaest 1984;56:57S.

27. Gallagher KP, Folts JD, Shebuski RJ, Rankin JHG, Rowe GG. Subepicardial vasodilator reserve in the presence of a critical coronary stenosis in dogs. Am J Cardiol 1980;46:67–73.

28. Roberts SL, Gilbert M, Tinker JH. Isoflurane has a greater margin of safety than halothane in swine with and without major surgery or critical coronary stenosis. Anesth Analg 1987;66:485–91.

29. Wegria R, Segers M, Keating RP, Ward HP. Relationship between the reduction in coronary blood flow and the appearance of electrocardiographic changes. Am Heart J 1949;38:90–6.

30. Waters DD, Da Luz P, Wyatt HL, Swan HJC, Forrester JS. Early changes in regional and global left ventricular function induced by graded reduction in regional coronary perfusion. Am J Cardiol 1977;39:537–43.

Tetanic Fade following Administration of Nondepolarizing Neuromuscular Blocking Drugs

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GIBSON FM, MIRAKHUR RK. Tetanic fade following administration of nondepolarizing neuromuscular blocking drugs. Anesth Analg 1989;68;759–62.

Fade in response to tetanic stimulation was studied following administration of atracurium 120 or 225 μg/kg, vecuronium 23 or 40 μg/kg, pancuronium 30 or 60 μg/kg, or d-tubocurarine 185 or 450 μg/kg. Ten patients received each dose and tetanic fade was measured at maximum block in the patients, who received the lower doses of the relaxants or at 10% recovery in those who received the higher doses. Fade during tetanic stimulation was generally similar in all the groups with the exception of the higher dose of pancu-ronium which showed a significantly greater fade in comparison with the higher doses of atracurium and d-tubocurarine. If fade in response to tetanic stimulation represents a prejunctional effect, the results from the present study suggest that neuromuscular blocking drugs cannot be differentiated with respect to their relative prejunctional effects by measurement of tetanic fade during established block after administration of clinically useful doses as used in the present study.

Key words: NEUROMUSCULAR RELAXANTS—d-tubocurarine, pancuronium, atracurium, vecuronium.

Fade in response to tetanic or train-of-four (TOF) stimulation following administration of non-depolarizing neuromuscular blocking agents is a characteristic of their activity. It has been suggested that this response is mediated by a prejunctional action (1–4). Furthermore it has been shown that different non-depolarizing relaxants exert different degrees of prejunctional effect, as shown by different degrees of TOF or tetanic fade (5–7). These studies have shown that d-tubocurarine has a greater prejunctional effect than pancuronium. Studies of tetanic fade in man have, however, been carried out using only small doses of relaxants (7) and it is not known whether this distinction persists during well-established block and when somewhat larger doses of relaxants, such as those administered clinically, are used. Moreover the relative degree of tetanic fade associated with the relatively newer relaxants atracurium and vecuronium is not well documented. The present study was designed to assess the fade in response to tetanic stimulation following administration of two different doses of atracurium, vecuronium, pancuronium, and d-tubocurarine to assess their relative prejunctional actions.

Methods

Eighty patients ASA physical status I or II aged 20–65 years were included in the study after obtaining their informed consent and Regional Ethical Committee approval. They were premedicated with oral diazepam and anesthetized with thiopental 5 mg/kg, nitrous oxide in oxygen, and fentanyl 4–8 μg/kg. Ventilation was assisted to maintain end-tidal carbon dioxide in the 4.5–5.0% range. No volatile agents were used during the study period. Neuromuscular monitoring was carried out by stimulation of the ulnar nerve at the wrist through cutaneous electrodes with supramaximal square wave impulses of 0.2 msec duration at a frequency of 0.1 Hz. The resultant force of adductor pollicis contraction was measured and recorded using a force displacement transducer and a neuromuscular function analyzer (Myograph 2000).

Following a period of stabilization of control twitch height, 10 patients each were randomly allocated to receive atracurium 120 or 225 μg/kg, vecuronium 23 or 40 μg/kg, pancuronium 30 or 60 μg/kg, or d-tubocurarine 185 or 450 μg/kg. These are the respective ED_{50} and ED_{95} (doses required for 50 and 95%
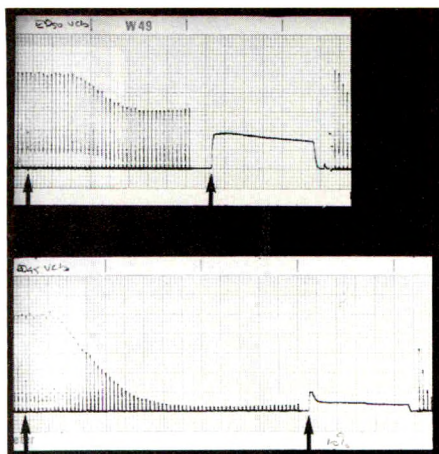
Figure 1. Representative records of two patients given ED_{50} (upper record) and ED_{95} (lower record) of vecuronium. The speed of the recording has been increased and the gain reduced in the upper recording during the tetanic stimulation. The two arrows represent the time of administration of the relaxant and the application of the tetanic stimulus.
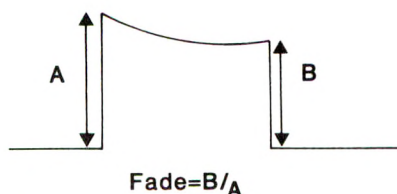
Fade=B/$_A$

Figure 2. Diagrammatic representation of peak tetanic height (A) and the tetanic fade (B/A).

block of the twitch height respectively) for these four agents, determined previously using a single dose method (8–10). The maximum block achieved in each patient was measured. Tetanic stimulation was applied at 50 Hz for 5 seconds at 10% recovery in patients who received a 95% blocking dose of relaxant or at the stage of maximum block in patients to whom a 50% blocking dose had been administered. A representative recording is shown in Fig. 1. Measurements were made of the height of the tetanic contraction at the start of the tetanus (A) and at the end of the 5-second period (B) and the tetanic fade (B/A) calculated (Fig. 2). Statistical analysis of the data was by analysis of variance followed by t-tests.

Results

The eight study groups were comparable in their physical characteristics apart from patients given ED_{50} doses of atracurium and ED_{50} doses of d-tubocurarine, who were relatively younger (Table 1). The average degree of neuromuscular block produced by the two different doses of each relaxant is

also shown in this table and is close to their expected effects.

The average peak tetanic contraction (A) and the degree of tetanic fade are given in Table 2. The peak contractions are given in mm and varied from 12.8 to 21.3 mm representing tensions of 1.28 to 2.13 kg following administration of the ED_{50} doses and from 2.4 to 3.5 mm representing tensions of 0.24 to 0.35 kg following the ED_{95} doses. There was no significant difference in either the peak tetanic height (A) or in the tetanic fade (B/A) in the groups given the ED_{50} doses of the relaxants. There was again no significant difference in the peak tetanic height in groups given ED_{95} of the agents. Analysis of variance, however, showed that significant differences were present in the tetanic fade between the groups given this dose of the relaxant. Further analysis by t-tests showed that this was due to significantly greater fade observed with this dose of pancuronium in comparison to d-tubocurarine and atracurium ($P < 0.05$).

Discussion

Fade in tetanic response is generally considered to represent a prejunctional effect of non-depolarizing neuromuscular blocking drugs (4,7,11,12) and the greater the fade, the greater is thought to be the relative prejunctional effect. These studies have shown, for example, that d-tubocurarine is associated with greater tetanic fade and consequently greater prejunctional effect than pancuronium.

A direct comparison of newer relaxants with each other or with pancuronium and d-tubocurarine using tetanic stimulation has not been reported, although it has been shown that atracurium and d-tubocurarine are associated with greater fade and consequently greater prejunctional effect than pancuronium and vecuronium during the onset of block using TOF stimulation (13). It was also suggested by Calvey and his co-workers (14) that atracurium acts at sites other than the postjunctional receptor. The results from the present study, however, suggest only minimal differences in tetanic fade between the relaxants both after establishment of the block and during recovery. Observation of greater fade with one dose of pancuronium is perhaps incidental and exceptional to the main findings of the present study.

The disparity of results cannot be explained by different modes of stimulation used, since results from studies of Stanec and Baker (7) using tetanic stimulation and those of Williams, Webb, and Calvey (6) and Brady et al. (13) using train-of-four (TOF) stimulation both showed the occurrence of greater

Table 1. Patient Characteristics and the Degree of Neuromuscular Block Produced

Drug		Dose μg/kg	n	Age Yr ± SD	Weight kg ± SD	Max block % ± SD
Atracurium	ED_{50}	120	10	30 ± 12.5	72 ± 13.6	53 ± 25.5
	ED_{95}	226	10	44 ± 18.0	71 ± 8.8	99 ± 1.6
Vecuronium	ED_{50}	23	10	45 ± 16.5	74 ± 15.2	48 ± 20.2
	ED_{95}	40	10	46 ± 16.9	65 ± 10.5	97 ± 3.6
Pancuronium	ED_{50}	30	10	53 ± 13.8	66 ± 14.1	62 ± 25.2
	ED_{95}	60	10	58 ± 11.2	76 ± 13.4	100
d-tubocurarine	ED_{50}	185	10	31 ± 16.6	64 ± 11.6	53 ± 23.0
	ED_{95}	450	10	49 ± 12.4	73 ± 10.3	99 ± 2.1

Table 2. Peak Tetantic Tension and Fade

	Peak tetanic tension mm ± SD		Tetanic fade mean ± SD	
	ED_{50}	ED_{95}	ED_{50}	ED_{95}
Atracurium	21.3 ±14.8	3.54 ±1.50	0.67 ±0.29	0.51† ±0.24
Vecuronium	16.3 ±13.6	2.43 ±0.48	0.75 ±0.29	0.34 ±0.19
Pancuronium	14.8 ±18.1	3.22 ±1.22	0.77 ±0.31	0.21*† ±0.08
d-tubocurarine	12.8 ±10.8	2.61 ±1.98	0.68 ±0.32	0.40* ±0.23

Differences significant between groups *$P < 0.05$; †$P < 0.005$.

fade with d-tubocurarine during the onset of block. The dosage of the relaxants used and whether the fade is measured during the onset or the offset of block may be the important determinants of fade. While Stanec and Baker (7) were able to demonstrate different degrees of fade between pancuronium and d-tubocurarine during tetanic stimulation, they were using only small doses of the relaxants, namely 1.0 and 3.0 mg respectively. On the other hand, Williams et al. (6), Pearce et al. (15), and Brady et al. (13) showed different degrees of fade with comparatively larger doses of relaxants using TOF stimulation during the onset of block. It appears that once a relatively profound block has been established, the variations between drugs in prejunctional and postjunctional receptor affinity disappear due to occupation of both types of receptors. This appears to be true not only in relation to tetanic stimulation as used in the present study, but also using TOF stimulation as shown by other workers (13,16,17).

It would have been reasonable to suggest that the results may have been influenced by the different durations of action of the relaxants particularly in the groups receiving the higher dose of the relaxants

where the assessments were made at 10% recovery. However this does not appear to be the case since d-tubocurarine and pancuronium have a similar duration, yet show quite different degrees of fade. The same is true for atracurium and vecuronium, which again have a similar duration of action but exhibit different degrees of tetanic fade.

In conclusion, the results of the present study show there to be little difference in the degree of tetanic fade following administration of atracurium, vecuronium, pancuronium, and d-tubocurarine in doses equivalent to their ED_{50} or ED_{95} doses, when fade is measured during well-established block. If fade in response to tetanic stimulation does represent a prejunctional effect, then the results from the present study suggest that it is not possible to differentiate between relative prejunctional effects of relaxants under such circumstances employing tetanic stimulation. It is likely that in clinical situations such differentiation can be made only during the onset of block since little difference in fade has been demonstrated between relaxants during recovery from block using TOF stimulation (16,17). It is possible that all the receptor sites, both postjunctional and prejunctional, are saturated once neuromuscular block has been well established.

References

1. Riker WF. Actions of acetylcholine on mammalian motor nerve terminals. J Pharmacol Exp Ther 1966;152:397–416.

2. Galindo A. Pre-junctional effect of curare: its relative importance. J Neurophysiol 1971;34:289–301.

3. Galindo A. The role of pre-junctional effects in myoneural transmission. Anesthesiology 1972;36:598–608.

4. Bowman WC. Pre-junctional and post-junctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–43.

5. Bowman WC, Webb SN. Tetanic fade during partial transmission failure produced by non-depolarising neuromuscular blocking drugs in the cat. Clin Exp Pharmacol Physiol 1976;3:545–55.

6. Williams NE, Webb SN, Calvey TN. Differential effects of myoneural blocking drugs on neuromuscular transmission. Br J Anaesth 1980;52:1111–5.

7. Stanec A, Baker T. Pre-junctional and post-junctional effects of tubocurarine and pancuronium in man. Br J Anaesth 1984;56:607–11.

8. Gibson FM, Mirakhur RK, Clarke RSJ, Lavery GG. Comparison of cumulative and single bolus dose techniques for determining potency of vecuronium. Br J Anaesth 1985;57:1060–2.

9. Gibson FM, Mirakhur RK, Lavery GG, Clarke RSJ. Potency of atracurium: a comparison of single dose and cumulative dose techniques. Anesthesiology 1985;62:657–9.

10. Gibson FM, Mirakhur RK. Dose-response curves for pancuronium and tubocurarine: a comparison of single and cumulative dose techniques. Eur J Anaesthesiol 1987;4:143–7.

11. Standaert FG. The actions of d-tubocurarine on the motor nerve terminal. J Pharmacol Exp Ther 1964;143:181–6.

12. Blaber LC. The pre-junctional actions of some non-depolarising blocking drugs. Br J Pharmacol 1973;47:109–16.

13. Brady MM, Clarke RSJ, Gibson FM, Mirakhur RK. Train-of-four fade during onset of neuromuscular block with atracurium, vecuronium, pancuronium and tubocurarine. Br J Pharmacol 1986;89:472P.

14. Calvey TN, Macmillan RR, West DM, Williams NE. Electromyographic assessment of neuromuscular blockade induced by atracurium. Br J Anaesth 1983;55:57S–62S.

15. Pearce AC, Casson WR, Jones RM. Factors affecting train-of-four fade. Br J Anaesth 1985;57:602–6.

16. Power SJ, Darowski MJ, Gallagher WJ, Jones RM. Fade profiles during spontaneous offset of neuromuscular blockade: gallamine and vecuronium compared. Br J Anaesth 1986;58:1328P.

17. O'Hara DA, Fragen RJ, Shanks CA. Reappearance of the train-of-four after neuromuscular blockade induced with tubocurarine, vecuronium or atracurium. Br J Anaesth 1986;56:1296–9.

Maintenance of Oxygenation during One-Lung Ventilation

Effect of Intermittent Reinflation of the Collapsed Lung with Oxygen

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MALMKVIST G. Maintenance of oxygenation during one-lung ventilation: effect of intermittent reinflation of the collapsed lung with oxygen. Anesth Analg 1989;68:763–6.

The aim of this study was to evaluate the effect on oxygenation of intermittent inflation with oxygen of the collapsed lung during one-lung ventilation (OLV). Sixteen patients were studied during pulmonary surgery. Balanced anesthesia with nitrous oxide and an inspired oxygen fraction of 0.5 was used. The control group (N = 8) had a median PaO_2 of 19.2 (range 11.2–30.2) kPa before OLV, and 10.2 (8.2–16.0) kPa after 9 minutes of OLV without further reduction in PaO_2 for another 10 minutes. In the treatment (inflation) group, the collapsed lung was manually inflated. with 2 liters of oxygen and was then immediately allowed to collapse again. This procedure was repeated every 5 minutes during OLV. PaO_2 increased more than 4 kPa following each inflation in seven patients. In the eighth, PaO_2 remained high throughout OLV. Although PaO_2 decreased between inflations, it never reached the level observed in controls during 19 minutes of OLV.

Key Words: ANESTHESIA—thoracic. VENTILATION—one-lung ventilation.

One-lung ventilation (OLV) during thoracotomy implies a risk of hypoxemia irrespective of ventilatory pattern used (1–4). To minimize this risk, several techniques have been suggested (5) including intermittent reinflation of the intentionally collapsed lung (6). However, the benefit of this modification of OLV has been questioned (5). The present study was designed to evaluate clinical usefulness and the effect of intermittent oxygen reinflation of the collapsed lung on oxygenation during OLV.

Methods and Patients

Sixteen patients (15 men) were studied during elective thoracotomy. Patients were randomly allocated to either OLV (control group, median age 66 years) or to OLV combined with intermittent reinflation of the upper lung (inflation group, median age 66 years). Age, smoking habits, diagnosis, site and type of surgery performed are listed in Table 1.

Anesthesia was induced with thiopental (2.5–6.5 mg·kg^{-1} intravenously). Succinylcholine was used to facilitate intubation with a Carlens double lumen tube. Meperidine was given intravenously after intubation (50–100 mg) and was used throughout the procedure for analgesia and in response to coughing or movements during surgery. Total doses of meperidine ranged from 350–800 mg. Fentanyl was substituted for meperidine during one case because of tachycardia. Relaxation with alcuronium (0.2–0.3 mg·kg^{-1} intravenously) was used to facilitate positioning of the patient on the operating table; further doses were rarely necessary. A Teflon cannula was inserted in the radial artery shortly after induction of anesthesia.

Ventilation with nitrous oxide at an inspired oxygen fraction (F_IO_2) of 0.5, as measured by a Siemens-Elema O_2 analyzer 110, was performed with a Servo Ventilator 900 B, (Siemens-Elema, Solna, Sweden). The ventilator was set at a rate of 20 min^{-1}, an inspiratory time of 25% and an end-inspiratory pause time of 10% of the respiratory cycle, and zero end-expiratory pressure. Inspired volume was adjusted to yield an end-tidal CO_2 tension of 4.5–5.5 kPa*) as measured by a Siemens-Elema CO_2 analyzer 930. Inspired volume was not changed subsequently, nor were any other ventilator settings.

All patients were operated on in the full lateral

*)kPa·7.502 = mm Hg.

Table 1. Patients

Patient	Age	Smoking[a]	Diagnosis	Side	Surgery
Control Group					
1	57	20	Adenosquamous cancer	L	Lobectomy (lower lobe)
3	63	50[b]	Squamous cancer	R	Explorative thoracotomy (inoperable)
6	66	40	Adenosquamous cancer	R	Lobectomy (upper lobe)
7	76	Never	Adenocarcinoma	L	Lobectomy (upper lobe)
10	67	20	Bronchioloalveolar cancer	L	Lobectomy (upper lobe)
11	65	50[b]	Adenosquamous cancer	R	Pneumonectomy
15	73	Nil for 8 yrs	Squamous cancer	R	Lobectomy (lower lobe)
16	38	Never	Carcinoid	L	Lobectomy (lower lobe)
Inflation Group					
2	65	20	Squamous cancer	L	Explorative thoracotomy (inoperable)
4	68	20	Squamous cancer	R	Pneumonectomy
5	54	60	Fibroma	R	Lobectomy (middle lobe)
8	58	Nil for 5 yrs	Silicosis	R	Wedge resection
9	74	75[b]	Bronchioloalveolar cancer	R	Bilobectomy (superior)
12	64	10	Squamous cancer	R	Bilobectomy (inferior)
13	67	50[b]	Mycobacteriosis	L	Segmental resections
14	67	10	Adenosquamous cancer	L	Lobectomy (lower lobe)

[a]Cigarettes per day; [b]grams of pipe tobacco per week. L = left; R = right.

decubitus position. During OLV the pleura was open, and the upper lung was allowed to collapse with its tube lumen open to the atmosphere. F_IO_2 of gases delivered to the lower lung was kept at 0.5. In patients in the inflation group, the upper lung was intermittently inflated manually with 100% oxygen with the use of a 2-liter anesthesia rubber bag (Fig. 1). The bag was emptied into the lung by a single compression immediately after which the inflation device was removed, and the lung was allowed to collapse again. Inflations were performed after 5, 10, and 15 minutes of OLV. All patients were closely followed for clinical signs of hypoxia, in the event of which oxygen inflations were to be delivered as needed. Surgery was not interrupted, and no branches of the pulmonary artery were ligated during the study period.

Blood was drawn from the arterial cannula for subsequent measurement of PaO_2 and $PaCO_2$. Samples were taken 1 minute before, 2, and 4 minutes after the start of OLV, and then 1 and 4 minutes after inflations (Fig. 2). In the control group, sampling was performed at corresponding times. Samples were immediately placed in melting ice and analyzed with an automated blood gas analyzer (IL 413, Instrumentation Laboratories, Lexington, MA) within 20 minutes of obtaining the last sample.

The significance of differences within groups was assessed with Wilcoxon's two-sided signed rank test. Differences between groups were tested with the two-sided Mann-Whitney's test.
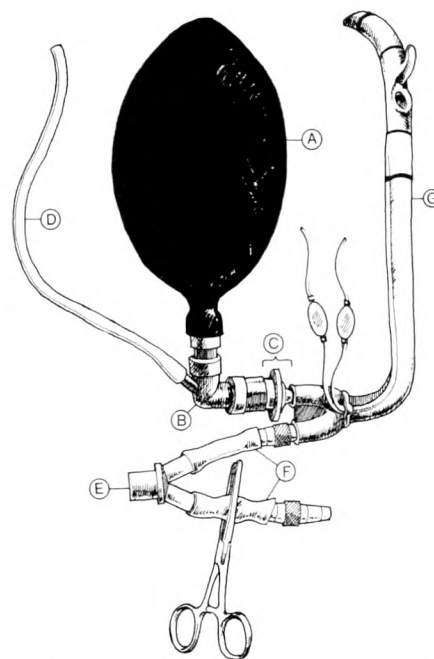
Figure 1. Device for reinflation of the upper lung during OLV shown in position. **A,** 2-liter anesthesia rubber bag. **B,** T-piece. **C,** Tube connector. **D,** From oxygen source. **E,** Ventilator connector with one of the limbs—**F**—clamped during OLV. **G,** Carlens tube.

Results

No clinical signs of hypoxia were detected and, therefore, no extra inflations of the upper lung with oxygen were performed in either group.

In the control group, median PaO_2, 19.2 (range 11.2–30.2) kPa before OLV, decreased to a minimum of 9.4 (7.6–10.8) kPa after 19 minutes of OLV ($P < 0.02$). PaO_2 decreased between the 2nd and 4th and
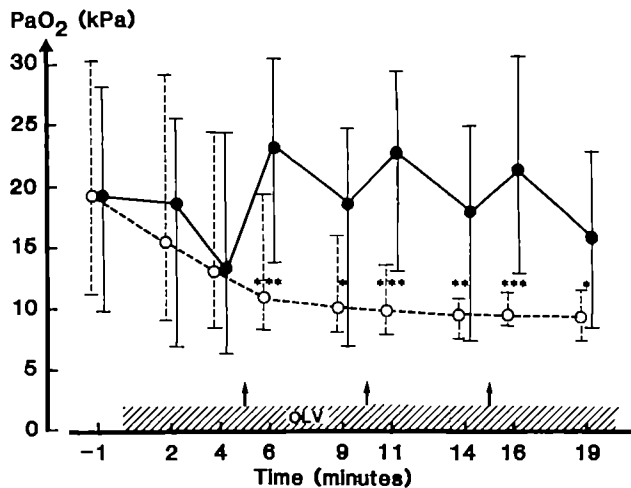
Figure 2. Arterial oxygen tension (PaO_2, median and range) in the control group (o- - -o) and inflation group (●——●). Arrows indicate inflations. P values for differences between groups denoted by $*P < 0.05$; $**P < 0.02$, and $***P < 0.01$.

the 4th and 6th minute ($P < 0.01$). The lowest PaO_2 (7.1 kPa) in this group was recorded after 16 minutes of OLV (patient no. 15).

In the inflation group, median PaO_2, 19.2 (range 9.8–28.1) kPa before OLV, decreased to a minimum of 12.9 (6.4–24.3) kPa before the first inflation, i.e., after 4 minutes of OLV ($P < 0.05$). In seven patients, PaO_2 had increased by 1 minute after each oxygen inflation and subsequently decreased to values that were, however, higher than corresponding values in the control group. In the eighth patient, no. 2, PaO_2 remained virtually constant throughout the investigation period (20.3–25.5 kPa). The lowest PaO_2 (6.4 kPa) in this group was recorded after 4 minutes of OLV in patient no. 8, who also had the lowest PaO_2 4 minutes after each inflation (7.0, 7.4, and 8.4 kPa).

Before the first inflation, PaO_2 did not differ between the groups. Thereafter, PaO_2 in the inflation group was always higher than at corresponding times in the control group (Fig. 2).

Median $PaCO_2$ was 4.7–5.4 kPa; there were no significant differences between groups and no significant changes within groups ($P > 0.05$).

Discussion

During OLV median PaO_2 was reduced with a considerable spread of values; this agrees with earlier reports on gas exchange during thoracic surgery (6–11). Hypoxemia during OLV is mainly due to right-left shunting through the collapsed lung (12). Differences between patients in arterial oxygenation during OLV may in part be explained by the preoperative state of the lung to be operated on (13); a lung in

which perfusion is already reduced affects PaO_2 less when it collapses during OLV than does a lung with normal perfusion. The major decrease in PaO_2 among controls occurred within 10 minutes of OLV; this agrees with previous studies in which nitrous oxide has been used (10,11).

Throughout the present study, patients were ventilated with an equal parts mixture of nitrous oxide and oxygen. An increase in F_IO_2 during OLV would probably have increased median PaO_2 (11,14), but not even an F_IO_2 of 1.0 can always protect the individual patient from impaired oxygenation (8). This is because an increase in F_IO_2 does not greatly improve PaO_2 in the presence of large right-left shunts (15). Avoidance of nitrous oxide during lung surgery, therefore, does not avoid the problem of hypoxemia during OLV.

No attempt was made to maintain inflation of the upper lung after the two-liter re-expansion had been accomplished, and no oxygen was delivered to the collapsing lung between inflations. Nevertheless, after the first inflation, PaO_2 values were at all times higher in the inflation group than in the control group. Thus, the beneficial effect of each inflation persisted to the next, even if at a gradually decreasing level. Intermittent reinflation (IR) of the upper lung with oxygen every 5 minutes increased PaO_2 in every patient except no. 2, who had cancer growing into pulmonary arterial branches at the hilum. Blood flow through the operated lung, therefore, was probably reduced, which explains why PaO_2 was unaffected by OLV and reinflations.

The IR interval of 5 minutes provided a PaO_2 of at least 9.4 kPa in all patients but no. 8 (see Results). This patient had silicosis, and it may be that a shorter IR interval is needed to maintain oxygenation during OLV in patients with restrictive lung disease. The usefulness of the pulse oximeter in lung surgery with OLV has been demonstrated (16), but such equipment was not available at the time of this study. Use of pulse oximetry would have allowed the timing of IR to be optimized.

A drawback with IR is that it may disturb the surgeon with whom the timing of inflations must be agreed. Because of this drawback and the lack of documentation of the effects of IR (5), the procedure has been recommended only hesitantly (17) or as a last resort (18). Instead, insufflation of oxygen at a constant positive pressure is advocated. In the author's department, this approach is also used, but it is supplemented with IR whenever needed as indicated by pulse oximetry.

In summary, this study demonstrates that during one-lung ventilation using balanced anesthesia with

an equal parts mixture of oxygen and nitrous oxide, manual reinflation with oxygen of the upper lung every 5 minutes substantially improves oxygenation.

References

1. Khanam T, Branthwaite MA. Arterial oxygenation during one-lung anaesthesia (1): a study in man. Anaesthesia 1973;28: 132–8.

2. Khanam T, Branthwaite MA. Arterial oxygenation during one-lung anaesthesia. Anaesthesia 1973;28:280–90.

3. Aalto-Setälä M, Heinonen J, Salorinne Y. Cardiorespiratory function during thoracic anaesthesia: a comparison of two-lung ventilation and one-lung ventilation with and without PEEP₅. Acta Anaesthesiol Scand 1975;19:287–95.

4. Katz JA, Laverne RG, Fairley HB, Thomas AN. Pulmonary oxygen exchange during endobronchial anesthesia: effect of tidal volume and PEEP. Anesthesiology 1982;56:164–71.

5. Benumof JL. One-lung ventilation and hypoxic pulmonary vasoconstriction: implications for anesthetic management. Anesth Analg 1985;64:821–33.

6. Björk VO, Carlens E. The prevention of spread during pulmonary resection by the use of a double-lumen catheter. J Thorac Surg 1950;20:151–7.

7. Nilsson E, Slater EM, Greenberg J. The cost of the quiet lung: fluctuations in PaO₂ when the Carlens tube is used in pulmonary surgery. Acta Anaesthesiol Scand 1965;9:49–55.

8. Kerr JH, Crampton Smith A, Prys-Roberts C, Meloche R, Foëx P. Observations during endobronchial anaesthesia II: oxygenation. Br J Anaesth 1974;46:84–92.

9. Capan LM, Turndorf H, Patel C, Ramanathan S, Acinapura A, Chalon J. Optimization of arterial oxygenation during one-lung anesthesia. Anesth Analg 1980;59:847–51.

10. Torda TA, O'Brien HD, McCulloch C, Tsui K. Venous admixture effect during one-lung anaesthesia. Anaesth Intensive Care 1972;1:45–53.

11. Torda TA, McCulloch CH, O'Brien HD, Wright JS, Horton DA. Pulmonary venous admixture during one-lung anaesthesia: the effect of inhaled oxygen tension and respiration rate. Anaesthesia 1974;29:272–9.

12. Alfery DD, Benumof JL, Trousdale FR. Improving oxygenation during one-lung ventilation in dogs: the effects of positive end-expiratory pressure and blood flow restriction to the nonventilated lung. Anesthesiology 1981;55:381–5.

13. Hurford WE, Kolker AC, Strauss W. The use of ventilation/perfusion lung scans to predict oxygenation during one-lung anesthesia. Anesthesiology 1987;67:841–4.

14. Tarhan S, Lundborg RO. Blood gas and pH studies during use of the Carlens catheter. Can Anaesth Soc J 1968;15:458–67.

15. Benatar SR, Hewlett AM, Nunn JF. The use of iso-shunt lines for control of oxygen therapy. Br J Anaesth 1973;45:711–8.

16. Brodsky JB, Shulman MS, Swan M, Mark JBD. Pulse oximetry during one-lung ventilation. Anesthesiology 1985;63:212–4.

17. Robertshaw FL. Anaesthesia for pulmonary surgery. In: Gray TC, Nunn JF, Utting JE, eds. General Anaesthesia. 4th ed. London: Butterworths, 1980:1325–49.

18. Benumof LD, Alfery DD. Anesthesia for thoracic surgery. In: Miller RD, ed. Anesthesia. 2nd ed. New York: Churchill Livingstone, 1986:1371–462.

Subclavian Perivascular Block: Influence of Location of Paresthesia

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Subclavian perivascular block: influence of location of
paresthesia. Anesth Analg 1989;68:767-71.

Subclavian perivascular block of the brachial plexus was used in 156 adult patients undergoing orthopedic hand and forearm surgery. The location of the elicited paresthesia prior to deposition of 30 ml of a solution containing 1% mepivacaine, 0.2% tetracaine and 1·200,000 epinephrine was recorded. Twenty minutes later the quality of the block in the distribution of the superior, middle and inferior trunks of the brachial plexus was evaluated. Anesthesia in each of the three trunks was compared with the three sites *where the paresthesia was elicited (superior, middle, or inferior trunk). A middle trunk paresthesia was the most successful in producing surgical anesthesia of all three trunks. A superior trunk paresthesia was the paresthesia most often elicited. It resulted in a significantly lower incidence of inferior trunk anesthesia than did a middle or inferior trunk paresthesia. Complications included arterial puncture (25.6%), Horner's syndrome (64.1%), and recurrent laryngeal nerve block (1.3%), with no instances of symptomatic phrenic block or symptomatic pneumothorax.*

Key Words: ANESTHETIC TECHNIQUES,
REGIONAL—brachial plexus.

The subclavian perivascular technique of brachial plexus block, as first described by Winnie and Collins in 1964 (1), has proven to be a valuable method of providing anesthesia for surgery of the hand and arm. In this technique, local anesthetic is deposited within the subclavian portion of the fascia enclosed space containing the brachial plexus and extending from the cervical transverse processes to beyond the axilla (2). The trunks of the brachial plexus are anesthetized as they lie within this subclavian perivascular space. The elicitation of paresthesia in the distribution of one of the trunks of the plexus is the most commonly used method to determine correct needle placement within the brachial plexus sheath. Discrimination of which trunk has been stimulated is not routinely done. The concept of a continuous perineural brachial plexus sheath makes it logical to assume that this discrimination is unnecessary. Deposition of local anesthetic subsequent to a superior, middle, or inferior trunk paresthesia should result in adequate anesthesia because all are closely located and contained within the brachial plexus sheath. However, it has been our clinical impression that the

location of the elicited paresthesia is a critical factor in determining the final quality of the block. The purpose of this study was to correlate the distribution of anesthesia with the location of the elicited paresthesia. We will also note the incidence of complications associated with the technique.

Methods

The Institutional Review Board provided approval prior to initiation of the study. Included in the study were 156 ASA physical status I or II patients scheduled to undergo orthopedic hand and forearm surgery under brachial plexus anesthesia. After obtaining written informed consent, patients were instructed that they may feel an "electric shock" sensation in the arm and that they should verbally communicate the particular location on the arm where they felt it. The subclavian perivascular brachial plexus block was then carried out as follows: the patient was placed in the supine position with the head turned opposite to the side being injected. The lateral margin of the clavicular head of the sternocleidomastoid muscle was identified at the level of C6 (determined by noting the level of the cricoid cartilage). The index finger of the anesthesiologist's palpating hand was then rolled laterally across the anterior scalene muscle until the interscalene groove, between the anterior and middle scalene muscles,

Sensory Distribution of the
Three Trunks of the Brachial Plexus

Superior trunk
Middle trunk
Inferior trunk
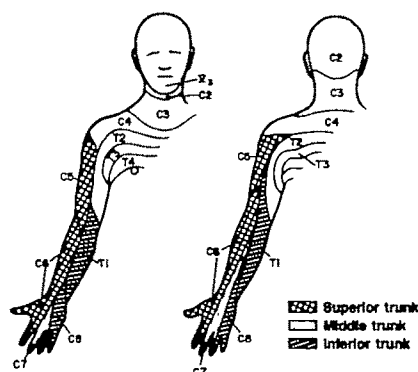
Figure 1. The superior trunk of the brachial plexus is formed by the roots of the fifth and sixth cervical nerves, the middle trunk is formed by the seventh cervical root, and the inferior trunk is formed by the roots of the eighth cervical and first thoracic nerves.

Table 1. Physical Characteristics of the Patients

Paresthesia Location	Age (yrs) mean ± SD	Height (inches) mean ± SD	Weight (kg) mean ± SD
Superior trunk	45.2 ± 15.7	66.8 ± 3.9	70.5 ± 15.7
Middle	45.1 ± 17.0	66.7 ± 4.7	67.9 ± 14.8
Inferior trunk	49.3 ± 16.7	65.8 ± 4.0	66.8 ± 15.7

was palpated. The groove was followed inferiorly as far as it could be easily palpated and a 22-gauge 4 cm regional block needle (short bevel) was inserted in the groove in a caudad direction. If the subclavian artery was encountered by the advancing needle (indicating the needle was too far anterior) the needle was withdrawn and reinserted in a more dorsal plane until a paresthesia was elicited. If the plexus was missed as the needle was inserted in the interscalene space, the first rib provided a shield to deter further needle advancement. When a paresthesia was elicited, an observer confirmed the paresthesia location with the patient by touching that particular portion of the arm. Thirty ml of a solution containing 1% mepivicaine and 0.2% tetracaine with 1·200,000 epinephrine was then injected. The dermatomes in which the elicited paresthesia was felt was recorded. Paresthesias involving C5 and C6 dermatomes represented stimulation of the superior trunk, C7 the middle trunk and C8, T1 the inferior trunk (Fig. 1). An immobile needle technique (3) was utilized in which a small bore intravenous extension tubing was placed between the needle and the syringe containing the anesthetic solution to provide stabilization of the needle during injection. The quality of anesthesia was determined by the presence or absence of sensation to pinprick 20 min following local anesthetic injection. After recordings of these data, supplemental injections in the axilla or at the elbow using <20 ml of 1% mepivicaine were done as necessary to insure adequate anesthesia at the surgical site.

Complications of the block were evaluated. The patients were examined for evidence of stellate ganglion block as evidenced by Horner's syndrome and recurrent laryngeal nerve block as evidenced by

hoarseness. The incidence of puncture of the subclavian artery and respiratory difficulty was also recorded. When indicated, inspiratory and expiratory x-rays of the upright chest were taken to determine the presence of phrenic nerve block or pneumothorax.

The incidence of successful anesthesia (loss of sensation to pinprick) in each of the three trunks was then compared between the three sites (superior, middle or inferior trunk) where the paresthesia was elicited and the local anesthetic solution injected. The relationship between arterial puncture and Horner's syndrome on the number of trunks anesthetized was examined. Statistical analyses were performed by chi square analysis with a P value of less than 0.05 considered statistically significant. Logistic regression was used to examine the relationship between the height of the patient and the number of trunks anesthetized (volume remaining constant).

Results

Physical characteristics of the patients are summarized in Table 1. There were no significant differences between the three groups in terms of age, height or weight.

Of the 156 patients, 100 patients (64%) had an initial paresthesia in the superior trunk distribution, 29 patients (19%) in the middle trunk distribution and 27 patients (17%) in the inferior trunk distribution. Superior trunk paresthesias were significantly more frequently elicited than were paresthesias of the middle or inferior trunks.

The incidence of successful anesthesia of the superior trunk was 94.0%, 96.6%, and 85.2% when a superior, middle, and inferior trunk paresthesia respectively were elicited (Fig. 2). The frequency of superior trunk anesthesia was not a function of the trunk in which the initial paresthesia was elicited.

The incidence of successful anesthesia of the middle trunk was 84.0%, 96.6%, and 92.6% when a superior, middle and inferior trunk paresthesia, respectively were elicited (Fig. 3). The frequency of

Anesthesia of the Superior Trunk
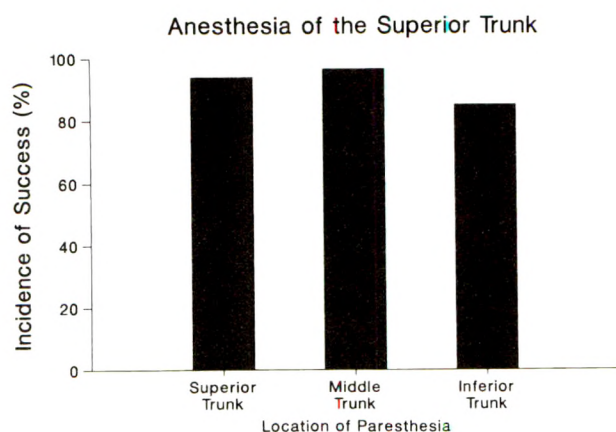
Figure 2. The incidence of successful anesthesia of the superior trunk was not significantly different depending upon the location of the elicited paresthesia.

Anesthesia of the Middle Trunk
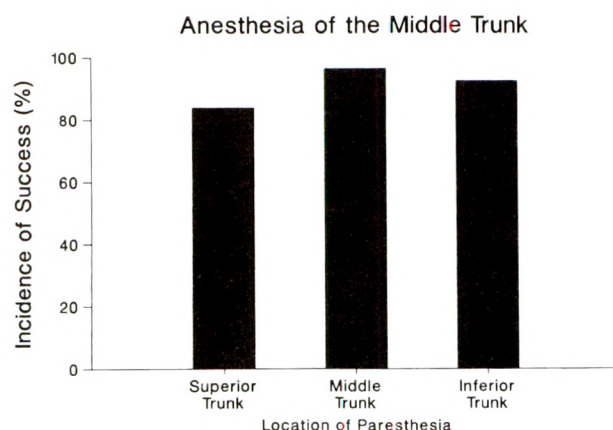
Figure 3. There was no significant difference in the incidence of successful anesthesia of the middle trunk if a superior, middle, or inferior trunk paresthesia was elicited.

middle trunk anesthesia was not a function of the trunk in which the initial paresthesia was elicited.

The incidence of anesthesia of the inferior trunk, however, was significantly dependent upon the location of the initial paresthesia. A superior trunk paresthesia resulted in a significantly lower incidence of inferior trunk anesthesia than did middle ($P < 0.001$) or inferior trunk paresthesias ($P < 0.023$). The incidence of successful anesthesia of the inferior trunk was 62.0%, 93.1%, and 85.2% when a superior, middle, and inferior trunk paresthesia, respectively, were elicited (Fig. 4).

Data analysis demonstrated that the height of the patient did not correlate with the number of trunks anesthetized.

Complications are summarized in Figure 5. The subclavian artery was punctured in 25.6% of the blocks. There was no significant difference in the number of trunks anesthetized between patients in which the artery was punctured and in those in

Anesthesia of the Inferior Trunk
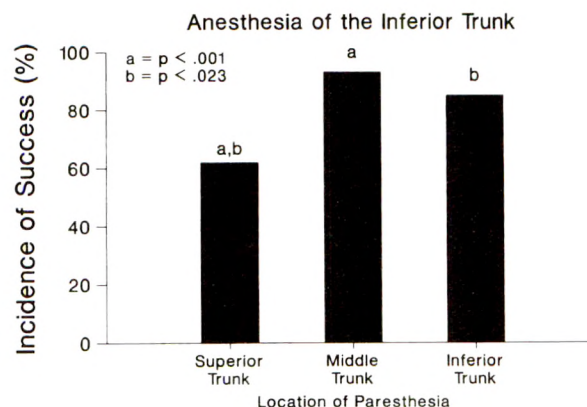
Figure 4. A superior trunk paresthesia resulted in a significantly lower incidence of inferior trunk anesthesia than did a middle ($P < 0.001$) or inferior trunk ($P < 0.023$) paresthesia.
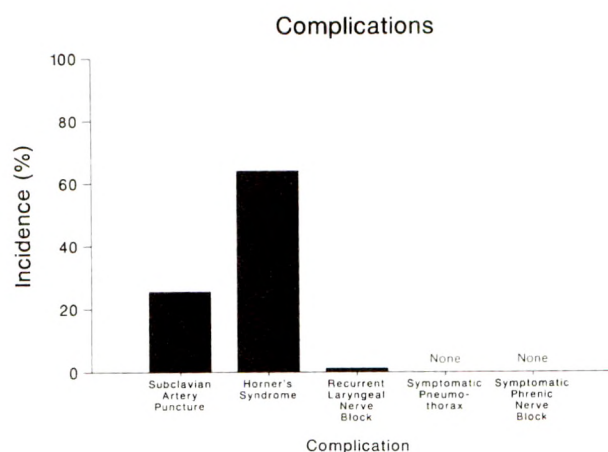
Complications

Figure 5. Complications associated with the technique included subclavian artery puncture (25.6%), Horner's syndrome (64.1%) and recurrent laryngeal nerve block (1.3%). No instances of symptomatic pneumothorax or symptomatic phrenic nerve block were seen.

which this complication did not occur. Horner's syndrome occurred in 64.1% of the patients. Its presence did not correlate with a difference in the number of anesthetized trunks. Block of the recurrent laryngeal nerve block occurred in 2 (1.3%) of the patients. No patients developed symptomatic pneumothorax or symptomatic phrenic nerve block.

Discussion

Smith first suggested that the effectiveness of a brachial plexus block depends on the distribution of the evoked paresthesia (4). In his study of 120 patients undergoing supraclavicular brachial plexus block, the success rate (93%) was greater if the paresthesia evoked by a low-power nerve stimulator was in the

distribution of the median nerve than when radial (81%) or ulnar nerve (76%) paresthesias were obtained. Paresthesias elicited by the subclavian perivascular technique, however, represent stimulation of the trunks of the brachial plexus. Therefore, rather than describing an elicited paresthesia in a peripheral nerve distribution as done by Smith, we chose to determine specifically which trunk of the brachial plexus represented the origin of the paresthesia. Like Smith, who proposed that a median nerve paresthesia may represent stimulation of the anterior division of the middle trunk, we found that a middle trunk paresthesia resulted in the highest incidence of success in blocking all three trunks of the brachial plexus. The explanation for this higher success rate is, according to Smith, that placement of the needle at the location of the middle trunk results in a more central deposition of the local anesthetic agent within the sheath of the plexus. As a result, this reduces the likelihood of the anesthetic solution being deposited outside the plexus following an inadvertent movement of the needle tip. It is probable, however, that inadvertent needle movement is not the only explanation for the greater success rate when a middle trunk paresthesia is obtained. Diffusion of the local anesthetic from the initial deposition site may also play a role. When the anesthetic solution is placed in the middle of the three trunks, it may diffuse more easily from this central location to anesthetize the superior and inferior trunks as well as the middle trunk.

The lowest incidence of successful inferior trunk anesthesia was found following a superior trunk paresthesia. This can most likely be explained by an inability of the local anesthetic to diffuse from the higher site of initial deposition at the superior trunk to the fibers of the inferior trunk which may be buried behind or beneath the subclavian artery. This lower success rate is particularly important when one considers that a superior trunk paresthesia was the most commonly elicited paresthesia in our study. This may be due to the anatomical placement of the trunks in a superior, middle, and inferior position. When the needle is placed in the neck in a directly caudad fashion at the level of C6, the superior trunk would be the most likely one encountered as the needle is advanced from its initial entry site. It is possible that insertion of the needle into the neck at a lower level directly behind the subclavian artery would result in a higher incidence of middle or inferior trunk paresthesias (rather than superior trunk). Further studies are necessary to confirm this hypothesis. Our results do indicate, however, that when anesthesia of the inferior trunk is necessary for the surgical procedure,

attempts should be made to avoid placement of the local anesthetic at the superior trunk. If the anesthetic solution is deposited following a superior trunk paresthesia, supplementation of the area supplied by the inferior trunk will frequently be required and therefore should be anticipated early.

The volume of local anesthetic used for the subclavian perivascular blocks was held constant in this study. It has been suggested previously that height is the single most important factor in determining local anesthetic volume for either sex at any age (5). This is due to the fact that the length of the brachial plexus sheath is directly dependent on the height of the patient. In our study, however, we found no correlation between the number of trunks anesthetized and the height of the patient. (56–76 inches). This could be due to the fact that 30 ml is a sufficient volume in adult patients to provide trunk anesthesia in the subclavian perivascular space. In the cases of incomplete block which occurred in our study, the problem may not have been one of insufficient volume, therefore, but rather of local anesthetic diffusion from the site of initial paresthesia to the other two trunks.

Subclavian artery puncture is recognized as a potential complication of subclavian perivascular as well as the more traditional techniques of supraclavicular brachial plexus block (1,6–9). Arterial puncture indicates that the needle has been placed anterior to the trunks of the plexus, but still lies within the brachial plexus sheath. Although occasionally resulting in hematoma formation, its occurrence is usually without sequelae (1,6). The incidence of arterial puncture in our study was 25.6%. This is comparable to an incidence of 32% found by Harley and Gjessing performing classical supraclavicular blocks (7). Dilution of the local anesthetic by arterial blood from local bleeding resulting from the puncture did not decrease the success rate of the block.

No patient in our study developed symptomatic pneumothorax. Pneumothorax with more traditional techniques of supraclavicular brachial plexus block may be more frequent. When utilizing the subclavian perivascular technique, however, the direction of the regional block needle remains parallel to that of the anterior and middle scalene muscles which invariably insert on the first rib (5). Therefore, if the plexus is missed as the needle is inserted in the interscalene space, the first rib will be encountered which prohibits further needle advancement and decreases the likelihood of puncturing the pleura. Routine postoperative chest x-rays to determine the incidence of asymptomatic pneumothoraces were not taken in this study. In order to ensure detection of a pneumotho-

rax, which may occur as late as 12–24 hrs following the block due to slow leakage of air from the lung, serial chest x-rays would have to be taken. Further studies are necessary, therefore, to determine if pneumothorax occurs more often than is clinically evident following subclavian perivascular block.

We also found no instance of symptomatic phrenic nerve block in our study. Unilateral phrenic nerve block may result in respiratory symptoms, as described by Kayerker et al. in a patient that received an interscalene brachial plexus block (10). When chest x-rays are examined routinely following the block, high incidences of phrenic nerve block have been reported. Knoblanche demonstrated a 67% incidence of phrenic block by fluoroscopic examinations in 15 patients within three hours following subclavian perivascular brachial plexus blocks (11). No patients in his series, however, developed respiratory symptoms related to the phrenic block. Farrar et al reported slightly lower incidences of 36, 36, and 38%, respectively, when routine chest x-rays were taken four hours following interscalene, subclavian perivascular, and Kulenkampff supraclavicular techniques of brachial plexus blocks (12). It appears, therefore, that phrenic nerve block is a common complication of brachial plexus blocks carried out above the clavicle but only infrequently leads to the development of respiratory symptoms or compromise.

Cervical plexus block leading to Horner's syndrome is also a possible complication of brachial plexus blocks performed above the clavicle (7,13,14). In our study we had a 64.1% incidence of Horner's syndrome. This complication was without adverse consequences and simply required reassurance to the patient that this was transient. Our data demonstrated that there was no significant difference in the number of trunks anesthetized between those patients which developed Horner's syndrome and in those in which this complication did not occur. This is in agreement with the concept that the syndrome may result not only from an improperly placed needle deep to the prevertebral fascia, but also from local anesthetic diffusion through the fascial covering of the brachial plexus to the sympathetic chain.

Recurrent laryngeal nerve block resulting in hoarseness occurred in two (1.3%) of our patients. This complication was also without adverse sequelae.

The two patients in our study with this complication had received blocks on the right side, and indeed recurrent laryngeal nerve block has been more commonly associated with right-sided blocks (5). This is due to the fact that the right recurrent laryngeal nerve is in close proximity to the subclavian artery as it loops around it in its ascent to the larynx, while the left recurrent laryngeal nerve loops around the aorta itself.

In conclusion, the location of the elicited paresthesia should be noted when performing subclavian perivascular blocks because the particular trunk stimulated may influence the development of anesthesia.

References

1. Winnie AP, Collins VJ. The subclavian perivascular technique of brachial plexus anesthesia. Anesthesiology 1964;25:353–63.
2. Winnie AP. Regional anesthesia. Surg Clin North Am 1975;54:861–92.
3. Winnie AP. An "immobile needle" for nerve blocks. Anesthesiology 1969;31:577–8.
4. Smith BE. Distribution of evoked paraesthesiae and effectiveness of brachial plexus block. Anaesthesia 1986;41:1112–5.
5. Winnie AP. Plexus Anesthesia. Perivascular Techniques of Brachial Plexus Block. Philadelphia: WB Saunders, 1983:208, 231, 237.
6. Bonica JJ, Moore DC, Orlov M. Brachial plexus anesthesia. Am J Surg 1949;98:65–79.
7. Harley N, Gjessing J. A critical assessment of supraclavicular brachial plexus block. Anaesthesia 1969;24:564–70.
8. Brand L, Papper EM. A comparison of supraclavicular and axillary techniques for brachial plexus blocks. Anesthesiology 1961;22:226–9.
9. dePablo JS, Diez-Mallo J. Experience with three thousand cases of brachial plexus block; its dangers. Ann Surg 1948;128:956–64.
10. Kayerker UM, Dick MM. Phrenic nerve paralysis following interscalene brachial plexus block. Anesth Analg 1983;62:536–7.
11. Knoblanche GE. The incidence and aetiology of phrenic nerve blockade associated with supraclavicular brachial plexus block. Anaesth Intensive Care 1979;7:346–9.
12. Farrar MD, Scheybani M, Nolte H. Upper extremity block: effectiveness and complications. Reg Anesth 1981;6:133–4.
13. Seltzer JL. Hoarseness and Horner's syndrome after interscalene brachial plexus block. Anesth Analg 1977;56:585–6.
14. Vester-Anderson T, Christiansen C, Hansen A, Sorensen M, Meisler C. Interscalene brachial plexus block: area of analgesia, complications and blood concentrations of local anaesthetics. Acta Anaesthesiol Scand 1981;25:81–4.

Intravenous Magnesium Sulfate Inhibits Catecholamine Release Associated with Tracheal Intubation

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JAMES MFM, BEER RE, ESSER JD. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation. Anesth Analg 1989;68:772-6.

The effects of pre-treatment with 60 mg/kg body weight magnesium sulfate intravenous on cardiovascular responses and catecholamine release associated with tracheal intubation were measured in 15 normal patients and in 15 saline solution pre-treated controls. Magnesium pre-treatment increased heart rate by 13 ± 3.9 beats/minute. After intubation, heart rate was unchanged in the magnesium group at 107.3 ± 3.6 beats/minute but increased in the control group to 120.9 ± 4.6 beats/minute (P < 0.05). Systolic blood pressure increased after intubation from 106.8 ± 3.1 to 121.0 ± 4.4 mm Hg in patients given magnesium and from 106.4 ± 3.12 to 145.1 ± 5.6 mm Hg in the control group (P < 0.05). Norepinephrine levels increased from 297.3 ± 20.9 pg/ml to a peak of 532.5 ± 30.1 pg/ml 2 minutes after intubation in the magnesium group. In controls, norepinephrine levels increased from 273.3 ± 39.1 mg/ml to 944.6 ± 68.7 pg/ml (P < 0.05 for differences between groups). Epinephrine levels were unchanged from baseline after magnesium but in controls increased from 113.9 ± 19.5 to 279.6 ± 92.3 pg/ml (P < 0.05) We conclude that magnesium sulfate attenuates the catecholamine mediated responses after tracheal intubation.

Key Words: IONS—magnesium. . INTUBATION—tracheal.

It is well known that laryngoscopy and tracheal intubation produce marked increases in pulse rate and blood pressure (1). This response is associated with the release of catecholamines in large amounts (2,3). There are various techniques by which this intubation-related stress response can be attenuated, all of which depend on reduction in input stimuli or the blockade of adrenergic responses. These methods include the use of lidocaine topically or intravenously (4); the administration of beta-adrenergic blocking drugs (1); the use of direct-acting vasodilators (5); and use of large doses of opiates, notably fentanyl and alfentanil (6). All of these techniques have disadvantages related to either cardiovascular or respiratory depression; none directly inhibits the release of catecholamines.

Magnesium blocks the release of catecholamines from adrenergic nerve terminals and from the adrenal gland in vitro (7,8). Increased serum magnesium levels may also inhibit the release of catecholamines in humans in whom catecholamine excess is present (9). The ion has relatively minor cardiovascular side effects at moderate blood levels (10), and its only respiratory depressant effect is related to its well-known ability to potentiate the action of the non-depolarizing neuromuscular blocking drugs (11). Magnesium reduces the pressor response to intubation in women with pregnancy-induced hypertension (12) and may well be of benefit in other circumstances. The purpose of this study is to investigate the ability of magnesium to control cardiovascular disturbances and inhibit the release of catecholamines at the time of intubation in otherwise healthy subjects.

Methods

The study was approved by the Ethics Committee of Hillbrow Hospital and the University of Witwatersrand and all patients gave informed consent.

Patients studied were ASA I-II men aged between 19–51 years booked for elective surgery in which the anesthetic technique would require tracheal intubation. Patients were randomly allocated to one of two groups with 15 patients in each group.

All patients were premedicated with diazepam 10 mg orally 1 hour pre-operatively. An intravenous cannula was inserted into one forearm for infusion of drugs, and a central venous line was placed via an antecubital vein for blood sampling. Anesthesia was induced with thiopental, titrated until the eyelash reflex was lost. In Group A patients, a 50% solution of magnesium sulfate ($MgSO_4$) 60 mg/kg body weight was then injected intravenously over 1 minute. Group B subjects received an equivalent volume of saline solution also over 1 minute. Subjects in both groups were then given succinylcholine 1 mg/kg body weight intravenously. Tracheal intubation was performed 60 seconds after the administration of succinylcholine by an operator who was blinded as to the patient's group. Blood samples for measurement of serum magnesium and plasma catecholamine concentrations were taken immediately prior to induction, immediately before intubation, immediately after intubation, and 2 and 5 minutes after intubation.

Tubes with blood samples for plasma catecholamine measurement were immediately placed on ice. Samples were centrifuged at 3,000 revolutions/minute for 10 minutes at 4°C. Aliquots of the serum were stored at −70°C for not longer than 1 week. Fractionated serum catecholamine concentrations were determined with use of reversed-phase high-performance liquid chromatography with electrochemical detection and an internal standard (13,14). The lower limit of sensitivity of this method is 10 pg/ml.

Standard electrocardiogram (ECG) leads were monitored throughout the procedure and blood pressure was monitored noninvasively with use of an automatic oscillotonometric device that recorded the blood pressure every 60 seconds. Heart rate was also recorded every 60 seconds. Statistical analysis was performed with the use of Student's t test for unpaired samples to detect differences, if any, between the groups. Significance was defined as ($P < 0.05$). Results are reported as mean ± 1 SEM.

Results

Serum Magnesium. Baseline serum magnesium concentrations were 0.85 ± 0.24 mmol/l in Group A and 0.81 ± 0.31 mmol/l in Group B. In Group A serum magnesium levels increased to 2.95 ± 0.56 mmol/liter after intubation and remained unchanged in Group B.

Cardiovascular System. Induction of anesthesia produced no significant changes in heart rate and blood pressure in either group. In the magnesium group,
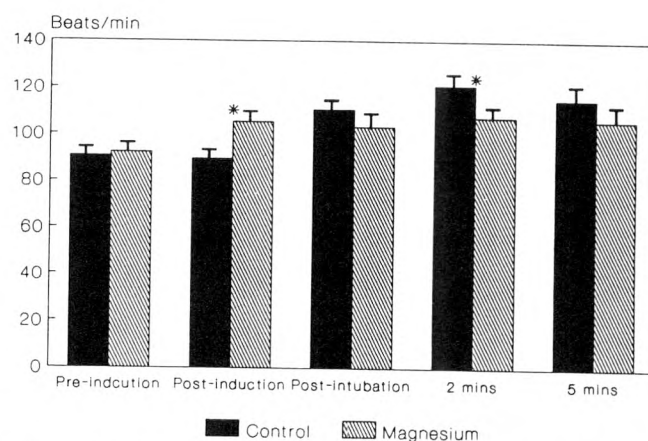
Figure 1. Changes in heart rate with and without magnesium. *$P < 0.05$ for differences between groups; T −1SEM.
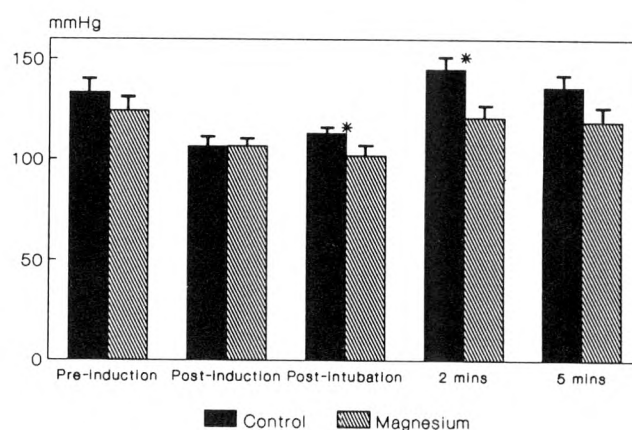
Figure 2. Changes in systolic blood pressure with and without magnesium. *$P < 0.05$ for differences between groups; T −1 SEM.

the injection of magnesium produced an initial increase in heart rate of 13 ± 3.9 beats/minute; in the control group, there was no significant change in heart rate from the baseline level ($P < 0.05$). After intubation, heart rate increased by 30.9 beats/minute 2 minutes after intubation in the control group, whereas in the magnesium group, heart rate remained virtually unchanged from post-magnesium values. The difference between groups at 2 minutes after intubation was significant at the 0.05 level (Figure 1).

Changes in systolic blood pressure are summarized in Figure 2. Induction of anaesthesia produced a small decrease in systolic and diastolic arterial blood pressure in both groups, but neither magnesium nor saline solution produced significant further changes. Immediately after intubation, systolic blood pressure increased in the control group but not in the magnesium group, the difference between the groups at this point being significant at the 0.05 level. Two minutes after intubation, systolic blood pressure increased
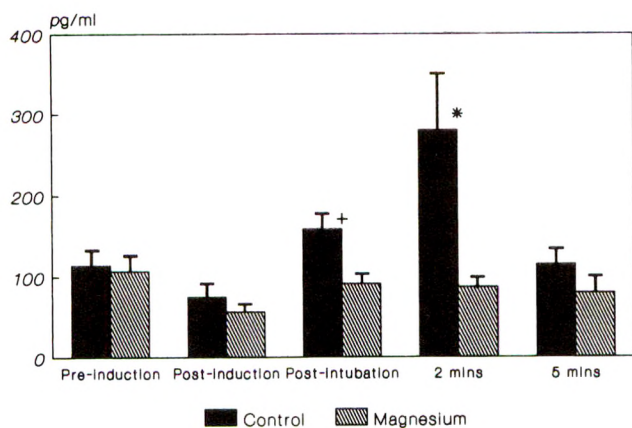
Figure 3. Changes in noradrenaline levels with and without magnesium. $†P < 0.01$ for differences between groups; $*P < 0.05$ for differences between groups; T −1 sem.
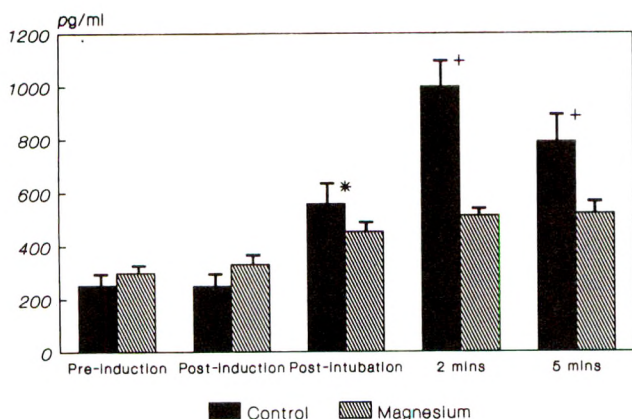
Figure 4. Changes in adrenaline levels with and without magnesium. $†P < 0.01$ for differences between groups; $*P < 0.05$ for differences between groups; T −1 sem.

slightly in the magnesium group toward baseline levels, but in the control group systolic blood pressure increased to above baseline levels ($P < 0.01$ for differences between groups). Diastolic blood pressures showed similar changes.

Catecholamines. Changes in catecholamines are summarized in Figures 3 and 4. Norepinephrine levels on arrival in the operating room were similar in the two groups and were not significantly altered by induction of anesthesia. After intubation, norepinephrine levels in the control group were significantly greater ($P < 0.05$) than those in the magnesium group, which were not significantly different from baseline values. Two minutes after intubation, the norepinephrine levels showed a further increase in Group B with a small, nonsignificant increase in Group A. The difference between groups was highly significant ($P < 0.01$), and this difference persisted at the 5-minute post-intubation measurement. Epineph-

rine values decreased slightly in both groups after induction of anesthesia. After intubation, epinephrine levels increased in Group B but not in Group A ($P < 0.01$). Two minutes after intubation, Group A epinephrine levels remained at baseline values whereas those in Group B remained elevated ($P < 0.05$). Five minutes after intubation, epinephrine levels in the two groups were not significantly different and had decreased to post-induction values in both groups (Figure 4).

Discussion

Calcium exerts a major role in stimulus-response coupling, including the release of catecholamines from the adrenal gland and adrenergic nerve terminals in response to sympathetic stimulation (15). Magnesium, because it competes with calcium for membrane channels, has been described as the physiological calcium antagonist (16) and can modify many calcium-mediated responses. The ability of magnesium ions to inhibit the release of catecholamines from both the adrenal gland and peripheral adrenergic nerve terminals has been known for over 25 years (7) and is now well established in laboratory experiments (8,17–19). However, until recently, no clinical use has been made of this potentially valuable phenomenon. The use of magnesium in conditions where catecholamine excess is prevalent, such as in tetanus (20) and phaeochromocytoma (21), has recently been described, and the ability of magnesium infusions to lower catecholamine levels in a patient with tetanus has been demonstrated (9). The present study shows that magnesium can significantly attenuate the output of catecholamines at the time of tracheal intubation and thus reduce the severity of cardiovascular disturbances.

The cardiovascular effects observed in this study were particularly interesting. It might be expected that magnesium would slow the atrial rate by inhibiting the calcium mediated depolarizing current in pacemaker tissue, an effect that has been demonstrated in isolated animal hearts (22). However, in the intact animal the ability of magnesium to inhibit the release of acetylcholine from the vagus nerve predominates (23) and, therefore, the overall effect is the mild increase in heart rate seen in this experiment. Despite this initial increase in heart rate, there was no further increase in heart rate after intubation in the magnesium group. Although heart rate in the control group was considerably less than that in the magnesium group prior to intubation, the heart rate after intubation in the control group was significantly

higher than in the magnesium group. This was presumably due to the fact that epinephrine levels in the magnesium group did not increase above baseline values, whereas in the control group there was a significant increase in epinephrine levels.

The vasodilator effects of magnesium (11,22–27) are characterized by a mild and transient decrease in blood pressure associated with peripheral vasodilatation and a consistent increase in cardiac index (10,28). Magnesium also reduces the responsiveness of vascular smooth muscle to norepinephrine stimulation (27). In the present study, increases in both systolic and diastolic blood pressure were less in the magnesium group than in the control group. In neither group was the release of norepinephrine completely prevented, but the norepinephrine levels in the magnesium group were significantly lower than those in the control group. The improved control of blood pressure in the magnesium group was probably, therefore, due to a combination of vasodilatory effects of the ion and inhibition of catecholamine release. It might be argued that magnesium is producing its effect by a central sedative mechanism, but this is unlikely as magnesium crosses the blood-brain barrier with difficulty and has little or no central sedative effect even at much higher serum levels than those used in the present study (29).

The actions of magnesium in protecting against the potentially harmful cardiovascular effects of tracheal intubation are probably not superior to the actions of the potent short-acting opiate agents, fentanyl and alfentanil. Alfentanil in particular shows considerable promise in this regard (30). However, the use of opiates has been associated with muscle rigidity, bradycardia, hypotension, and respiratory depression. In circumstances in which these complications may be undesirable, magnesium could be a useful alternative. A serum magnesium level of 2–4 mmol/liter at the time of endotracheal intubation may be particularly valuable in the hypertensive pregnant patient. Magnesium has also been shown to reduce fasciculations (31) and potassium release (32) after succinylcholine, and these actions combined with the cardiovascular control that can be achieved by the use of magnesium may be of value.

Magnesium does not appear to prolong the duration of action of succinylcholine (31,33), but the interaction between magnesium and the non-depolarizing relaxants must be borne in mind if this technique is to be used in combination with these latter drugs. If this combination is to be used, then the dosage of relaxant should be reduced (11,33). There is currently no data available as to the effect that $MgSO_4$ might have on the onset time or intensity of block achieved when non-depolarizing relaxants are used to facilitate tracheal intubation.

A final intriguing possibility is that combinations of short-acting opiates and magnesium may offer good cardiovascular control at lower doses of both agents and therefore with fewer side effects. This possibility remains to be evaluated.

References

1. Siedlecki J. Disturbances in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of the sympathetic system. Anaesth Resusc Intens Ther 1975;3:107–10.

2. Russell WJ, Morris RG, Frewin DB, Drew SE. Changes in plasma catecholamine concentrations during endotracheal intubation. Br J Anaesth 1981;53:837–9.

3. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G. Plasma catecholamine responses to tracheal intubation. Br J Anaesth 1983;55:855–9.

4. Stoelting RK. Blood pressure and heart rate changes during short duration laryngoscopy for tracheal intubation. Influence of viscous intravenous lidocaine. Anesth Analg 1978;57:197–9.

5. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 1979;58:116–9.

6. Stanley TH, Berman L, Green O, Robertson D. Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary-artery operations. Anesthesiology 1980;53:250–3.

7. Douglas WW, Rubin RP. The mechanism of catecholamine release from the adrenal medulla and the role of calcium in stimulus-secretion coupling. J Physiol 1963;167:288–310.

8. Lishajko F. Releasing effect of calcium and phosphate on catecholamines, ATP, and protein from chromaffin cell granules. Acta Physiol Scand 1970;79:575–85.

9. Lipman J, James MFM, Erskine J, Plit ML, Eidelman J, Esser JD. Autonomic dysfunction in severe tetanus: magnesium sulfate as an adjunct to deep sedation. Crit Care Med 1987;15:987–8.

10. James MFM, Cork RC, White JF, Dennett JE. Cardiovascular effects of magnesium sulphate in the baboon. Magnesium 1987;6:314–324.

11. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 1970;32:23–8.

12. Cork RC, James MFM. Magnesium pre-treatment at C-section for pregnancy induced hypertension (Abstract). Anesth Analg 1985;64:202.

13. Krstulovic AM. Investigations of catecholamine metabolism using high-performance liquid chromatography. J Chromatogr 1982;229:1–34.

14. Causon RC, Carruthers ME. Measurement of catecholamines in biological fluids by high-performance liquid chromatography. J Chromatogr 1982;229:301–9.

15. Rasmussen H. The calcium messenger system. N Engl J Med 1986;314:1164–70.

16. Iseri LT, French JH. Magnesium: Nature's physiologic calcium blocker. Am Heart J 1984;108:188–93.

17. Dandavino A, Woods JR, Murayama K, Brinkman CR III, Assali NS. Circulatory effects of magnesium sulphate in nor-

motensive and renal hypertensive pregnant sheep. Am J Obstet Gynecol 1977;127:769–74.

18. Kirpekar SM, Misu Y. Release of noradrenaline by splenic nerve stimulation and its dependence on calcium. J Physiol (Lond) 1967;188:219–34.

19. George AJ, Leach GDH. Differential effect of alterations on the calcium and magnesium concentrations on the responses to sympathetic amines in the perfused rat mesentry. Br J Pharmacol 1971;42:663–4.

20. Von Euler VS, Lishajko F. Effects of Mg^{++} and Ca^{++} on noradrenaline release and uptake in adrenergic nerve granules in different media. Acta Physiol Scand 1973;89:415–22.

21. James MFM, Manson EDM. The use of magnesium sulphate infusions in the management of very severe tetanus. Intensive Care Med 1985;11:5–12.

22. Turlapaty PDMV, Carrier O. Influence of magnesium on calcium induced responses of atrial and vascular muscle. J Pharmacol Exp Ther 1973;187:86–98.

23. Somjen GG, Baskerville EN. Effect of excess magnesium and vagal inhibition and acetylcholine sensitivity of the mammalian heart in situ and in vitro. Nature 1968;217:679–80.

24. James MFM. Magnesium sulfate in pheochromocytoma. Anesthesiology 1985;62:188–9.

25. Altura BM, Altura BT. Magnesium and vascular tone and reactivity. Blood Vessels 1978;15:5–16.

26. Kelly HG, Cross HC, Turton MR, Hatcher JD. Renal and cardiovascular effects induced by intravenous infusion of magnesium sulphate. Can Med Assoc J 1960;82:866–71.

27. Farmer JB, Campbell IK. Calcium and magnesium ions: influence on the response of an isolated artery to sympathetic nerve stimulation, noradrenaline and tyramine. Br J Pharmacol 1967;29:319–28.

28. Mroczek WJ, Lee WR, Davidow ME. Effect of magnesium on haemodynamics. Angiology 1977;28:720–4.

29. Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects by intravenous administration of magnesium sulphate. J Pharmacol 1966;154:652–9.

30. Crawford DC, Fell D. Effects of alfentanil on the pressor and catecholamine responses to tracheal intubation. Br J Anaesth 1987;59:707–12.

31. De Vore JS, Asrami R. Magnesium sulfate prevents succinylcholine induced fasciculations in toxemic patients. Anesthesiology 1980;52:76–7.

32. James MFM, Cork RC, Dennett JE. Succinylcholine pretreatment with magnesium sulfate. Anesth Analg 1986;65:373–6.

33. Baraka A, Yazigi A. Neuromuscular interaction of magnesium with succinylcholine-vecuronium sequence in the eclamptic parturient. Anesthesiology 1987;67:806–8.

Right Heart Dysfunction, Pulmonary Embolism, and Paradoxical Embolization during Liver Transplantation

A Transesophageal Two-Dimensional Echocardiographic Study

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ELLIS JE, LICHTOR JL, FEINSTEIN SB, CHUNG MR, POLK SL, BROELSCH C, EMOND J, THISTLETHWAITE JR, ROIZEN MF. Right heart dysfunction, pulmonary embolism, and paradoxical embolization during liver transplantation: a transesophageal two-dimensional echocardiographic study. Anesth Analg 1989;68:777–82.

In 16 adult patients, we performed continuous intraoperative two-dimensional transesophageal echocardiography (2DTEE) to help elucidate the mechanism of myocardial dysfunction that accompanies liver transplantation. In 4 of the 16 patients "paradoxical" motion of the interventricular septum consistent with right ventricular failure was seen. An additional three of the 16 patients showed right atrial enlargement and right-to-left deviation of the interatrial septum. Two patients showed evidence of paradoxical embolization (one of whom had right ventricular and right atrial enlargement), and a third patient (who had right atrial enlargement) embolized a large right atrial thrombus into the pulmonary circulation. Two-dimensional transesophageal echocardiography demonstrated that isolated right ventricular failure might account for some of the hemodynamic instability seen during liver transplantation. Venous, pulmonary, and paradoxical embolization of air and thrombi documented by transesophageal echocardiography likely contribute to right heart failure.

Key Words: LIVER, TRANSPLANTATION. SURGERY, LIVER TRANSPLANTATION. MEASUREMENT TECHNIQUES, ECHOCARDIOGRAPHY. HEART, ECHOCARDIOGRAPHY.

Improvements in surgical technique, the intraoperative use of venous bypass, and cyclosporin immunosuppressive therapy have all contributed to the more frequent use of liver transplantation as a therapeutic option for patients with end-stage liver disease. These operations are of long duration (five to fifteen hours) and are performed on patients who often present with multisystem organ failure. Massive, rapid transfusions of many blood volumes are the rule, further complicating management of these patients.

Unique hemodynamic changes accompany the different stages of orthotopic liver transplantation. The release of tense ascites, temporary occlusion of the inferior vena cava, and reperfusion of the donor liver all cause profound and characteristic alterations in cardiovascular homeostasis. Measurements made with Swan-Ganz catheters have been used to manage and describe these processes (1), but there are limitations to their accuracy in assessing left ventricular preload (2). We have used two-dimensional transesophageal echocardiography to monitor cardiovascular performance during liver transplantation and to obtain insights into the accompanying circulatory pathophysiology.

Materials and Methods

This study was approved by our Clinical Investigations Committee. Sixteen adult patients undergoing

liver transplantation were included in the study after consenting to our data collection protocols. Anesthesia, induced with thiamylal and followed by succinylcholine, was maintained with oxygen, air, isoflurane, and fentanyl, with pancuronium for relaxation. Monitoring consisted of measurements obtained from radial and pulmonary artery catheters and from pulse oximeters. Blood products were rapidly administered through two 8 French introducers with the aid of a rapid volume infusion device. Non-heparinized veno-venous bypass was used during occlusion of the inferior vena cava to preserve venous return and to facilitate the surgical procedure. Five minutes before perfusion of the donor liver, patients were empirically treated with sodium bicarbonate (1 mEq/kg), 50% dextrose (1 ml/kg), and calcium chloride (20 mg/kg). This treatment regimen, with the addition of 10 units of regular insulin, was repeated immediately after reperfusion.

After endotracheal intubation, we inserted a gastroscope tipped with a 3.5-MHz echocardiographic probe (Diasonics, Milpitas, CA) into the esophagus and connected it to a Diasonics 6400 Ultrasonograph. The echocardiogram was monitored continuously, and qualitative judgments of cardiac filling volumes and contractility guided patient management. Echocardiographic views were obtained at two levels: 1) the long-axis four-chamber view to evaluate the interaction of left and right ventricles and detect possible venous air embolism, and 2) the short-axis view to evaluate left ventricular size, contractility, and segmental wall motion. Adjustments in transducer position were occasioned by upper abdominal retraction and our intentional variation from long-axis to short-axis views. We attempted to obtain short-axis views as identical as possible during these adjustments, using the mid-papillary muscles as landmarks. We recorded echocardiographic sequences of interest on one-half inch VHS videotape for off-line analysis by a cardiologist who was unaware of clinical conditions.

In nine patients, standard transthoracic echocardiograms were obtained perioperatively for clinical management with the results noted. The presence of cardiac pathology on available postmortem examinations was also noted.

Results

Patient Characteristics

Table 1 summarizes the demographic features of our patient population. Collectively, these patients represent a critically ill group. Two had preoperative respiratory failure requiring mechanical ventilation and 6 presented with renal insufficiency (as documented by a serum creatinine greater than 2.0 mg/dl). Nine of the patients were encephalopathic preoperatively. Nine of the 16 patients underwent routine transthoracic echocardiography in the perioperative period. The findings, summarized in Table 1, included pericardial effusions in four patients, significant tricuspid regurgitation in two patients, and decreased right ventricular systolic function in two others.

Intraoperative Wall Motion Abnormalities

Four patients (1, 5, 9, and 15) had transesophageal echocardiographic evidence of abnormal motion of the interventricular septum. In patient 1, the septal abnormality noted before incision resolved after the release of tense ascites. Paracentesis was accompanied by an increase in left ventricular end-diastolic diameter from 3.3 to 4.2 cm. This septal wall motion abnormality recurred after reperfusion of the donor liver. In three patients (5, 9, and 15), new interventricular septal wall motion abnormalities were identified after graft reperfusion.

In three additional patients (6, 10, and 16), without evidence of abnormal ventricular wall motion, bulging of the interatrial septum from right-to-left was seen, suggesting a positive right-to-left pressure gradient at the atrial level.

Only one patient (7) had evidence of left ventricular decompensation as evidenced by severe global hypokinesis during the procedure; this improved after an infusion of dobutamine was begun.

Air Emboli and Thromboemboli

In all patients, spontaneous echogenic contrast material was seen in the right heart during thermodilution cardiac output determinations, during venous bypass, and at the time of donor liver reperfusion.

In two patients (5 and 12) paradoxical embolization occurred, as spontaneous echogenic contrast material was identified in the left heart at the time of reperfusion of the donor liver (Fig. 1). We believe this echogenic contrast represented air and/or microthrombi.

Transesophageal echocardiography revealed a large thrombus in the right atrium of patient 6 (Fig. 2) during venous bypass. The thrombus later disappeared, presumably embolized into the pulmonary circulation. This patient also demonstrated a very

Table 1. Clinical Information on Patients Undergoing Liver Transplantation with Transesophageal Echocardiographic Monitoring

Patient	Age	Diagnosis	Preoperative				Transthoracic echocardiography	Paradoxical embolization	Abnormal septal wall motion	Additional tee abnormalities
			Renal insufficiency	Respiratory failure	Prothrombin time	Blood volumes replaced				
1	28	Budd-Chiari syndrome	+	+	18.8	1	Dilated, hypokinetic RV	–	+	None
2	56	Chronic active hepatitis B	–	–	15.1	1	Large PA, pericard effusion, MR, TR	–	–	None
3	27	Fulminant hepatitis	+	+	23.4	4	Small pericard effusion; septal WMA	–	–	None
4	36	Cryptogenic cirrhosis	–	–	16.4	16	N/A	–	–	None
5	45	Chronic active hepatitis B	–	–	13.5	12	N/A	+	+	RA>LA, RV>LV, Hypovolemic LV
6	48	Chronic active hepatitis B	+	–	14.6	13	N/A	–	–	RA>LA, RA thrombus, Hypovolemic LV
7	40	Cryptogenic cirrhosis	–	–	16.5	5	RA>LA, paradoxical IVS, poor LV fn, dilated RV	–	–	Global hypokinesis, improved after dobutamine infusion
8	40	Cryptogenic cirrhosis	+	–	14	20	Small pericardial eff, mild MR, small LV	–	–	None
9	21	Fulminant hepatitis	–	–	36.4	5	N/A	–	+	None
10	62	Primary biliary cirrhosis	–	–	14.4	3	Mod AS, gradient=64 mm Hg, mild LVH, MR, TR	–	–	RA>LA, Small pericardial effusion
11	36	Hemangiosarcoma	–	–	11.9	0.5	N/A	–	–	None
12	46	Cryptogenic cirrhosis	+	–	16.9	3	WNL	+	+	None
13	35	Chronic active hepatitis B	–	–	12.1	2	N/A	–	–	None
14	14	Cryptogenic cirrhosis	–	–	13.8	1	Small pericardial effusion	–	–	None
15	46	Primary graft failure	+	–	17.7	2	WML	–	+	None
16	24	Fulminant non-A, non-B hepatitis	–	–	35.9	0.4	N/A	–	–	RA>LA, Hypovolemic LV

AS, aortic stenosis; fn, function; IVS, interventricular septum; LV, left ventricle; LVH, left ventricular hypertrophy; MR, mitral regurgitation; N/A, no available; RA, right atrium; RA>LV, right atrium larger than left atrium and bulging right-to-left; RV, right ventricle; RV>LV, right ventricle larger than lef ventricle and bulging right-to-left; PA, pulmonary artery; TR, tricuspid regurgitation; WNL, normal; WMA, wall motion abnormality.

thin intraatrial septum, which bulged into the left atrium. The central venous pressure rose acutely to 38 mm Hg after graft reperfusion, despite systemic hypotension; severe acute hepatic congestion at this time necessitated phlebotomy. Transesophageal echocardiography at that time revealed a small, hyperkinetic left ventricle and a markedly dilated right heart.

Echocardiographic and Pulmonary Capillary Wedge Pressure as Determinants of Preload

We observed an inconsistent relationship betweer pulmonary capillary wedge pressure (PCWP) anc filling volumes. Figure 3, for example, demonstrate end-diastolic frames from patient 9 during venou bypass. The two frames were recorded 30 minute
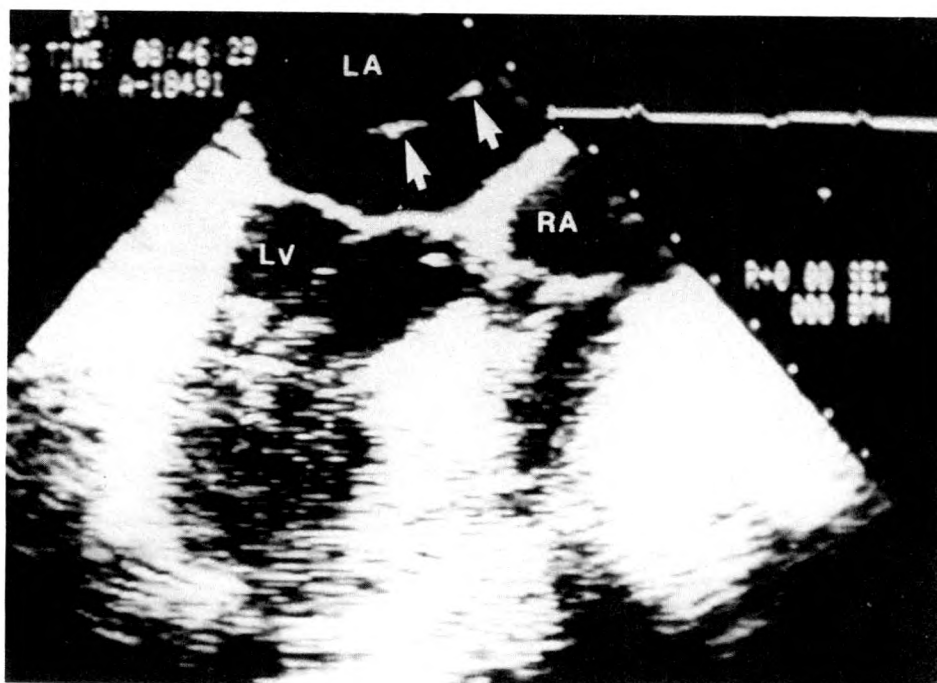
Figure 1. Evidence of paradoxical embolization (arrow) in left atrium (LA) of patient 5. Left ventricle (LV), right atrium (RA).
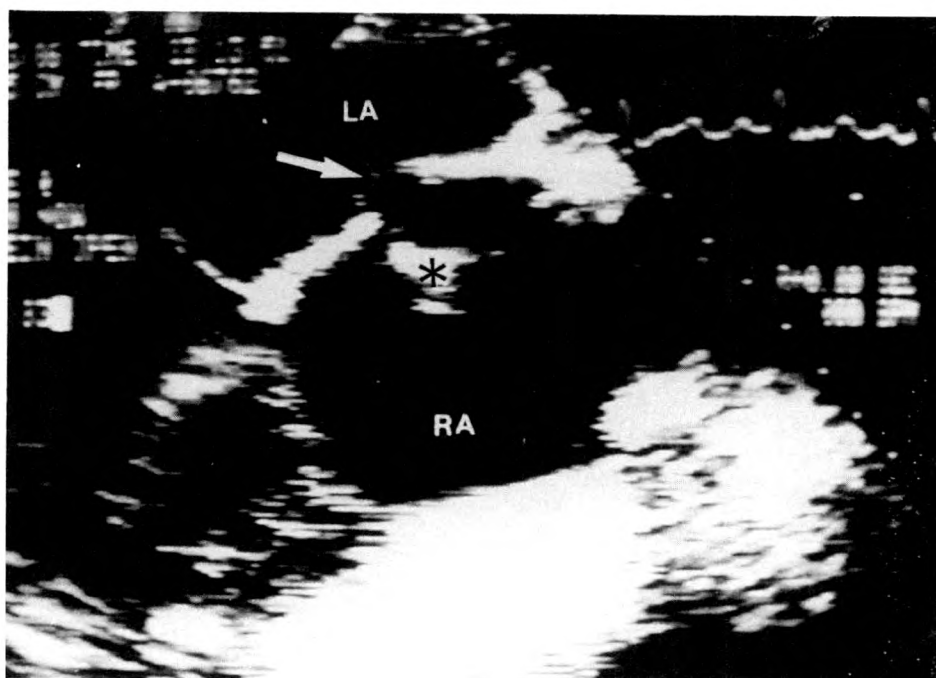
Figure 2. Large thrombus (asterisk) in right atrium (RA) of patient 6, which later embolized into the pulmonary circulation. The intraatrial septum, which is thinned (arrow), bulges in a right-to-left direction. (LA = left atrium).

apart, during which time pulmonary artery pressures increased greatly. While the two frames reveal almost identical end-diastolic dimensions, the PCWP was 20 mm Hg during the first frame, and 40 mm Hg during the second.

Postmortem Examinations

Autopsies were obtained in two patients. Other than the presence of air in the right side of the heart after reperfusion, neither of these patients had any echo-
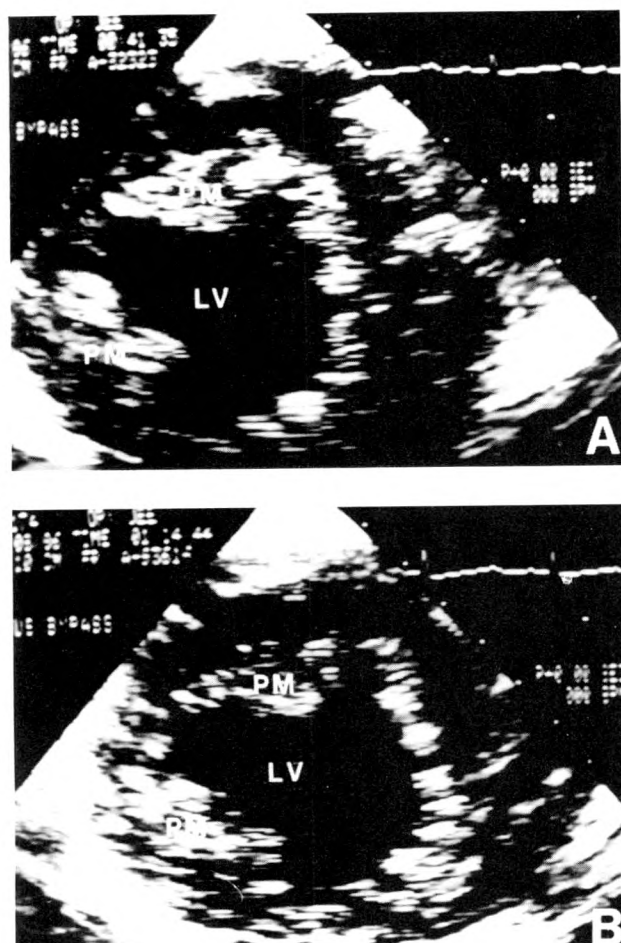
Figure 3. Two end-diastolic frames of short-axis views of the left ventricle (LV), 30 minutes apart, from patient 9 during venous bypass. While end-diastolic areas appear nearly identical, pulmonary capillary wedge pressure doubled from 20 mm Hg (A) to 40 mm Hg (B) during this interval. (PM = papillary muscle).

cardiographic abnormalities. Postmortem examination of the heart revealed right ventricular hypertrophy and cardiomegaly with a thickened pulmonary outflow tract in patient 8. Patient 4 had pulmonary vascular changes consistent with ARDS (adult respiratory distress syndrome) and pericarditis, but no intrinsic myocardial pathology.

Both patients (5 and 12) who experienced paradoxical air embolus died, but postmortem examinations were not available; the presence of a probe-patent foramen ovale could not be determined.

Discussion

Cardiovascular Response to Donor Liver Reperfusion

Severe hypotension at the time of reperfusion of the donor liver is a well-described phenomenon. It has been variously attributed to hypovolemia or myocardial depression (3). Carmichael et al. (1) using data from Swan-Ganz catheterization, described a pattern of hypotension associated with elevated (pulmonary artery pressure) PAP and PCWP and concomitant decreases in (cardiac output) CO. They interpreted these results as being consistent with acute left heart failure at the time of reperfusion, purportedly due to the release of vasodepressor substances from the donor liver.

In our series, care was taken to flush the donor liver of ischemic metabolites by infusing an albumin solution into the donor liver and discarding the effluent immediately before reperfusion. Also, in an attempt to prevent life-threatening hypotension and hyperkalemia, we routinely administered calcium chloride, bicarbonate, and glucose/insulin at the time of reperfusion of the donor liver. We did so empirically, theorizing that we might also be treating citrate intoxication. Citrate intoxication is a documented cause of decreased left ventricular contractility in patients undergoing liver transplantation (4). We did not believe it safe to examine the circulatory responses to reperfusion in the absence of this empiric treatment. While aggressive therapy may have obscured left ventricular dysfunction due to metabolic causes, our data suggest that right heart failure, due to pulmonary embolism of air and thrombi, plays a role in the hypotension seen after reperfusion of the donor liver.

Embolic Events

Echocardiography enabled us to see microembolization and macroembolization. Similar macroembolization has been observed using transesophageal echocardiography during total hip replacement with associated increases in pulmonary artery and wedge pressures and decreases a PaO_2 and mean arterial pressure (5).

The finding of a dilated right heart on echocardiography and passive congestion of the liver on visual inspection implies acute right heart failure, as does the presence of abnormal interventricular septal wall motion (6). This may limit left ventricle filling by diminishing pulmonary venous return. In several patients, transthoracic Doppler echocardiography performed preoperatively revealed tricuspid regurgitation. "Functional" tricuspid regurgitation, secondary to annular dilatation, may contribute further to dangerous congestion of the new liver and a decreased right ventricular ejection fraction. Tricuspid regurgitation also makes the determination of cardiac output by thermodilution inaccurate.

Humoral factors may be involved in the pathogenesis of pulmonary hypertension, further increasing right heart work; short periods of partial veno-venous bypass increase pulmonary elaboration of thromboxane (7) and cause pulmonary hypertension in sheep. The use of non-heparinized venous bypass may contribute to the formation of thrombi, such as the one we observed (Fig. 2). Others have used heparinized bypass to avoid such thrombotic complications, but this was accompanied by massive hemorrhage and an unacceptably high mortality rate (8). Still, the formation of thrombi in the venous bypass machine may be reduced by keeping flows greater than one liter/minute; in the future, the use of heparin-bonded bypass tubing may reduce the risk of thromboembolism (8). Despite these problems, the use of venous bypass during hepatectomy offers substantial advantages that probably outweigh the risks of thrombosis. Its use during liver transplantation has been shown to preserve venous return and cardiac preload and output, decrease transfusion requirements, and lower the incidence of renal failure and mortality in the first month after liver transplantation (8).

Paradoxical Air Embolus

Two of our patients (5 and 12) showed transesophageal echocardiographic evidence of paradoxical embolization, possibly due to intracardiac shunting. The acute elevation in right ventricular afterload imposed by pulmonary emboli may cause elevated right heart pressures, allowing the reversal of the normal intraatrial gradient and facilitating paradoxical embolization of air or microthrombi across an atrial septal defect or a probe-patent foramen ovale (9). In four of our patients (5, 6, 10, and 16), intraoperative echocardiography demonstrated bulging of the interatrial septum in a manner consistent with elevated right atrial pressures (Fig. 3), and another patient (7) demonstrated this pattern on preoperative echocardiography.

Others have documented evidence suggesting paradoxical air embolus during hepatic transplantation. Starzl et al. (10) reported that nine of 48 patients in their early experience had neurologic complications consistent with cerebral air embolus. The potential for right-to-left shunts may exist in these patients, even in the absence of intracardiac shunts. Cirrhotics are prone to develop intrapulmonary shunts (11), and echocardiographic contrast studies have been used to document their presence (12).

In summary, these cases and observations confirm the common phenomenon of pulmonary embolism

during liver transplantation and demonstrate its sequelae: right ventricular and right atrial encroachment on left heart filling, and paradoxical emboli. Pericardial effusions and tricuspid regurgitation are frequently seen, and may also compromise cardiovascular function. We have also shown that left ventricular pumping function is not generally impaired in this small series of patients when generous doses of calcium chloride are given.

References

1. Carmichael FL, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation: cardiovascular and metabolic alterations and their management. Anesth Analg 1985;64:108–16.

2. Hansen RM, Viquerat CE, Matthay MA, Wiener-Kronish JP, DeMarco T, Bahtia S, Marks JD, Botvinick EH, Chatterjee K. Poor correlation between pulmonary arterial wedge pressure and left ventricular end-diastolic volume after coronary artery bypass graft surgery. Anesthesiology 1986;64:764–70.

3. Joseph WL, Fonkalsrud EW, Longmire WP jr. Vasodepressive effects of the venous effluent following canine liver allotransplantation. J Surg Res 1968;8:367–72.

4. Marquez J, Martin D, Virji MA, Kang YG, Warty VS, Shaw B jr, Sassano JJ, Waterman P, Winter PM, Pinsky MR. Cardiovascular depression secondary to ionic hypocalcemia during hepatic transplantation in humans. Anesthesiology 1986;65:457–61.

5. Roewer N, Beck H, Kochs E, Kremer P, Schroder E, Schulte AM, Esch J. Detection of venous embolism during intraoperative monitoring by two-dimensional transesophageal echocardiography. Anesthesiology 1986;63:A169.

6. Kaul S. The interventricular septum in health and disease. Am Heart J 1986;112:568–81.

7. Peterson MB, Huttemeier PC, Zapol WM, Martin EG, Watkins WE. Thromboxane mediates acute pulmonary hypertension in sheep extracorporeal perfusion. Am J Physiol 1982;243:H471–H479.

8. Shaw BW, Martin DJ, Marquez JM, Kang YG, Bugbee AC jr, Iwatsnki S, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524–34.

9. Marshall WK, Bedford RF, Miller ED. Hemodynamics during anesthesia in the seated position. Anesth Analg 1982;61:201.

10. Starzl TE, Schneck SA, Mazzoni G, Aldrete JA, Porter KA, Schroter GPJ, Koep LJ, Putnam CW. Acute neurologic complications after liver transplantation with particular reference to intraoperative cerebral air embolus. Ann Surg 1978;187:236–40.

11. Krowka MJ, Cortese DA. Pulmonary aspects of chronic liver disease and liver transplantation. Mayo Clin Proc 1985;60:407–18.

12. Shub C, Tajik AJ, Seward JB, Dines DE. Detecting intrapulmonary right-to-left shunt with contrast echocardiography: observations in a patient with diffuse pulmonary arteriovenous fistulas. Mayo Clin Proc 1976;51:81–4.

Heat Generation as an Index of Exhaustion of Soda Lime

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TSUCHIYA M, UEDA, W. Heat generation as an index of exhaustion of soda lime. Anesth Analg 1989;68:783-7.

The wall temperatures of the absorptive chambers of a divided soda lime canister were measured in 70 patients to determine the relationship between the difference in temperature of the two chambers and CO_2 passage through the first chamber. CO_2 passage through the first chamber was detected when the temperature of the second chamber became equal to that of the first. A significant correlation $(R = 0.94; P < 0.001)$ was found between the magnitude of CO_2 passage through the first chamber and the difference in temperature between the chambers. When the maximal absorptive capacity of soda lime was reached, the pH of the surface of soda lime granules was still too high to change the indicator color. Exhaustion of soda lime is more reliably recognized by measuring wall temperatures of the chambers than by observing color change of the soda lime granules.

Key Words: EQUIPMENT, ABSORBER—heat generation.

Soda lime granules used in canisters to absorb CO_2 from anesthesia circuits contain a pH-sensitive dye to indicate its degree of exhaustion. However, unreliability of the color indicator has been reported (1-5). For example, the color change along the sides of the canister may not reflect the state of the absorbent throughout the canister since the expiratory gases pass along the sides more easily than through the center (1,2). In addition, a change in color from normal base to "exhausted" occurs rapidly when regenerated soda lime is used. Nevertheless, the color change of soda lime is still the most commonly used indicator of its exhaustion since, at present, there is no other simple and reliable technique. The increasing use of capnometry and mass spectrometry enables the inspired gas to be monitored for CO_2 content, and the color change may thus become a less important index for determining the state of exhaustion of soda lime. It would, however, be preferable to quantify the residual absorptive capacity so that the soda lime could be changed before it is completely exhausted.

Soda lime produces heat when it reacts with CO_2, and changes in the absorbent temperature occur much earlier than the changes in color of the indicator (6). We therefore investigated the relationship between the difference in heat production of two soda lime chambers arranged in series and their state of exhaustion to test the hypothesis that measuring the change in the temperature of the absorbent may be a more effective and more accurate means of quantifying the residual absorptive capacity than the indicator color.

Methods

The study protocol was approved by Kochi Medical School's Committee for the Protection of Human Subjects. The studies were performed in 70 adult patients (ASA physical status I and II) anesthetized with halothane, nitrous oxide, and oxygen. A canister, divided into two chambers, was filled with 1500 gm (2 × 750 gm) of Wakolime®, soda lime with ethyl violet as a pH indicator. A baffle ring at the bottom of the chamber prevented channeling of expired air along the canister wall. Fresh anesthetic gas was delivered at a flow rate of 4 liters/min to the breathing circuit of a circle system. The patients were ventilated mechanically at a tidal volume of 10-15 ml/kg to maintain the $PaCO_2$ between 36 to 44 mm Hg except during neurosurgical procedures (25 to 35 mm Hg). The peak partial pressure of CO_2 passing through the first chamber [$PPCO_2(I)$] was measured between the two absorptive chambers. End-tidal CO_2 ($PECO_2$) was measured at the tracheal tube with a capnometer
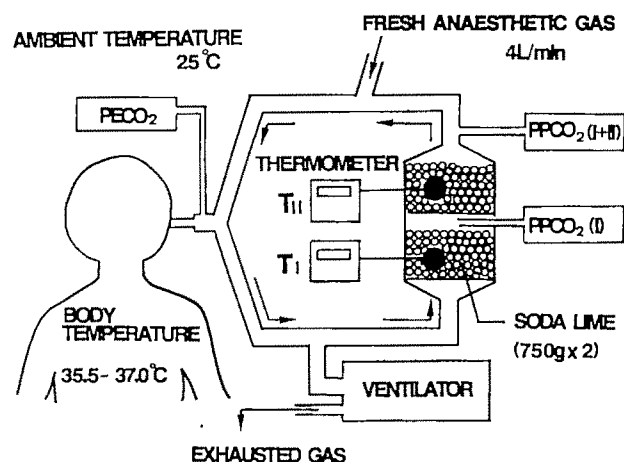
Figure 1. Breathing circuit used in this study. T_I, T_{II}: wall temperatures of the first and second absorptive chambers, respectively: $PPCO_2(I)$ is peak PCO_2 passage through the first absorptive chamber; $PPCO_2(I+II)$ is peak PCO_2 passage through the two absorbers in series.

using NEC SAN-EI 1H21A. The peak passage of PCO_2 through the two chambers in series [$PPCO_2$ (I+II)] was measured with a second capnometer (Hewlett–Packard 78345A) attached to the outlet of the canister. The changes in the wall temperature of the two chambers in series were calculated with two surface temperature sensing devices (TERUMO TF-DN). The changes in color of the soda lime were determined by observing the chambers (Fig. 1). All measurements were started one hour after the initiation of anesthesia.

Study 1

Twenty chambers in 10 canisters filled with fresh soda lime were used once a day. The changes in wall temperature of the absorber chambers, $PPCO_2(I)$, $PPCO_2(I+II)$, and the color were continuously and simultaneously monitored. In addition, the wall temperature of each of the 10 chambers in 5 canisters was recorded continuously on a two-channel recorder (SHIMADZU-112M). We defined that the maximal absorptive capacity was reached when the value of $PPCO_2(I+II)$ became 4–5 mm Hg.

Study 2

The pH of the surface of the soda lime was measured in 10 canisters with completely exhausted absorptive capacity. Soda lime was sampled from four colored and four uncolored portions of each of the chambers, and the surface pH was determined by placing the

wet sample on a pH test paper, DUOTEST®, pH 9.5–14.0, (Macherey-Nagell & Co.). The surface pH of fresh wet soda lime was determined in a similar manner.

Data are expressed as means ± SD. The statistical significance of differences between two mean values was tested by Student's t-test. P values of less than 0.05 were considered significant.

Results

The mean values of the age, body weight, and height of the patients were 46 ± 19 yr, 56 ± 11 kg, and 158 ± 12 cm, respectively.

Study 1

The cumulative time courses of the changes in temperature and color of the first and second chambers, and the CO_2 passage through the absorbents from one divided canister used in 9 patients are shown in Fig. 2. The time courses of those changes in 10 canisters are summarized in Fig. 3. During the early stage using fresh soda lime, the temperature of the first chamber stayed 2.7 ± 0.5°C higher than that of the second. As time went on, the temperatures of the two chambers became closer, and their relationship then reversed. The CO_2 passage through the first absorber was detected when the temperature of the second chamber equaled that of the first. The temperature of the second chamber exceeded that of the first before a change in color became apparent in the first chamber. The temperature difference between the chambers increased with a concomitant increase in CO_2 passage through the first absorbent. The CO_2 passage through the two chambers in series was then detected. The value of $PPCO_2(I+II)$ stayed between 1 to 2 mm Hg for several hours and thereafter increased as rapidly as 1 mm Hg per 5 to 10 min.

The color of the first chamber of 8 divided canisters used in 55 patients became purple, while the color of the second chamber did not change in any part of any of the 8 canisters. The color of the remaining 2 divided canisters used in 15 patients changed at the center on the core of the first absorbent, which was invisible from the outside. But the relationship between the wall temperature of the canister and $PPCO_2(I)$ of these 2 was the same as that of the other 8 canisters.

The relationship between the difference in temperature of the two chambers and $PPCO_2(I)$ was expressed by an exponential equation using the least-

Figure 2. Time course of the temperatures of the walls of the chambers and the peak PCO_2 passage through the absorbent ($PPCO_2$). One divided canister filled with fresh soda lime was used in 9 patients until the maximal absorptive capacity was reached, resulting in CO_2 rebreathing.
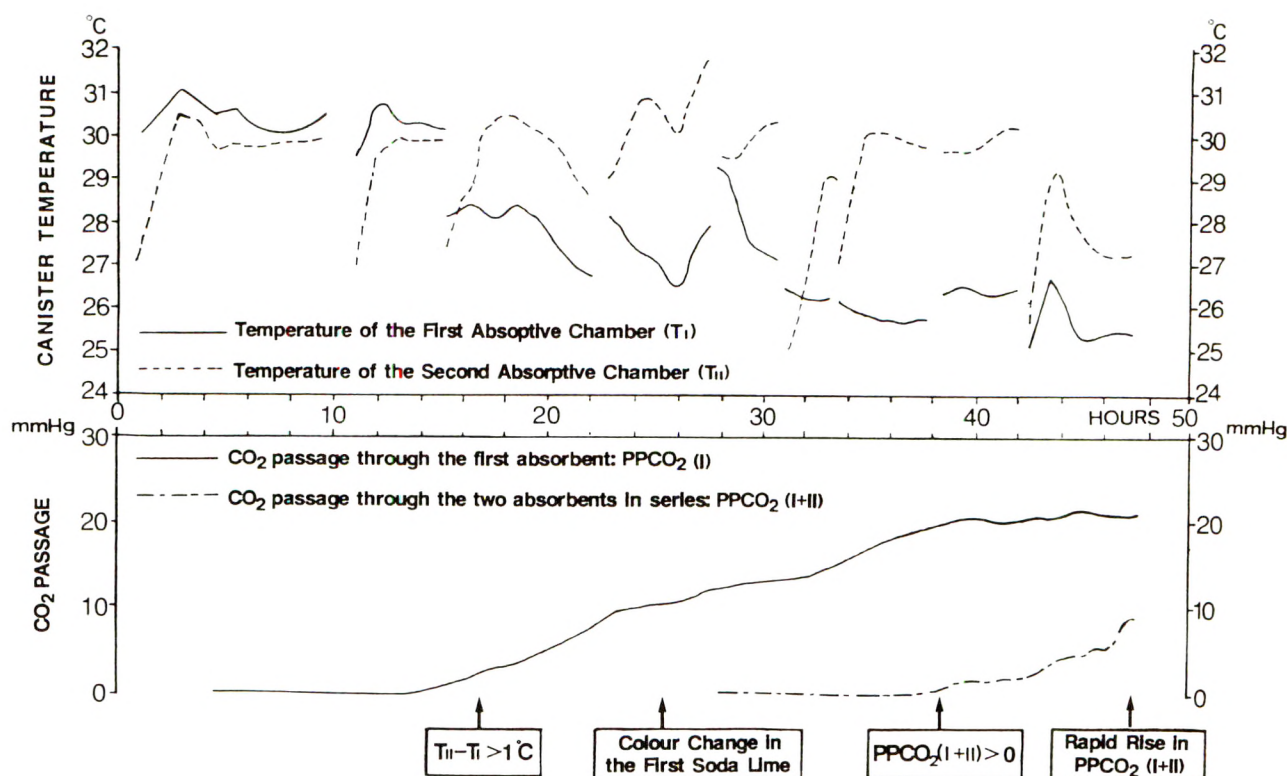
squares method. A significant positive correlation was found between the values of $PPCO_2(I)$ and those of the difference in temperature of the two chambers (Fig. 4).

Study 2

Figure 5 shows a histogram of the surface pH of the colored and uncolored portions of the exhausted soda lime. The mean values of the surface pH of colored soda lime granules and that of uncolored granules were 10.9 ± 0.6 and 12.9 ± 0.7, respectively. The surface pH of uncolored soda lime granules was significantly higher than that of the colored soda lime granules. The surface pH of fresh soda lime was above 14.0.

Discussion

The neutralization of one mole of CO_2 by soda lime produces heat equivalent to 13.7 kcal. The temperature of the central axis of the absorber at different levels in a canister represents the efficacy of CO_2 absorption at each level (6,7). The temperature at the center of the canister is consistently higher than at the periphery, yet the pattern of temperature change is similar at each level (8). The wall temperature of the absorber, lower than that of the central axis (6), is affected not only by CO_2 being absorbed but also by the surrounding room temperature. It is, however, much easier and more practical to measure the temperature of the wall of a soda lime canister instead of the central axis temperature within the canister during clinical anesthesia.

One of the most important findings in our study was that there was a significant correlation between the partial pressure of CO_2 passing through the first chamber and the difference in wall temperatures between the two chambers ($R = 0.94$; $P < 0.001$). It was confirmed that the relationships between the partial pressure of CO_2 passing through the first chamber and the difference in wall temperatures between the two chambers observed when the fresh gas flow rate was 4 liters/min were also the same when the fresh gas flow rate was 0.5 liters as well as 10 liters/min (data not shown). Once the temperature of the second chamber exceeded that of the first, the temperature of the first decreased as the temperature of the second increased. It is also important to point
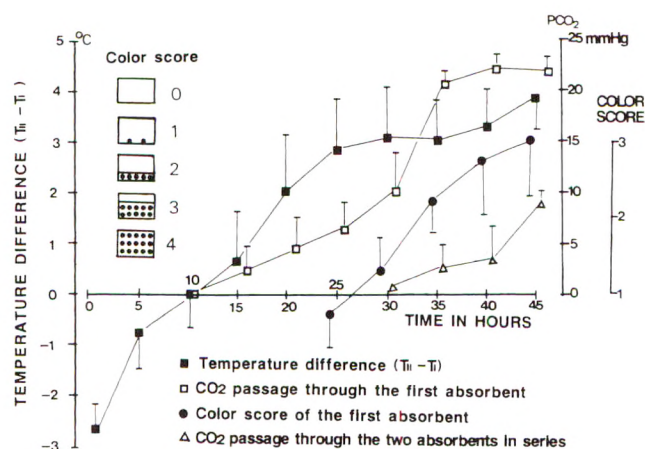
Figure 3. Summary of the time courses of the changes in wall temperatures and color of the chambers, and the peak PCO_2 passage through the absorptive chambers measured in 20 chambers in 10 canisters (mean ± SD). The indicator color changed in 8 of 10 canisters. T_I = wall temperature of the first absorptive chamber, T_{II} = wall temperature of the second absorptive chamber.
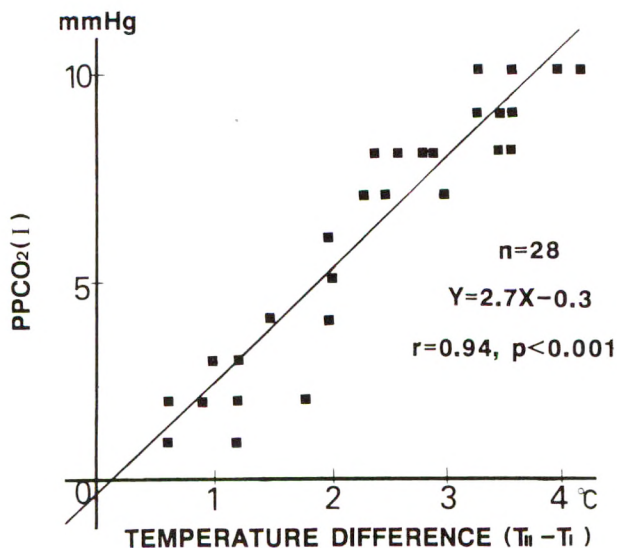
Figure 4. The peak PCO_2 passage through the first absorptive chamber ($PPCO_2(I)$) is plotted against the differences in temperature between the two chambers in series, where the temperature of the second chamber was higher than that of the first. T_I = wall temperature of the first absorptive chamber, T_{II} = wall temperature of the second absorptive chamber.

out that the temperature of the second chamber surpassed that of the first before there was any apparent color change in the first absorbent. Our findings represented strong evidence in support of our hypothesis that CO_2 passage through the first chamber can be readily and reliably surmised by measuring the wall temperature of the chambers.

The color indicator reflects the reduction of pH on the surface of soda lime granules caused by the
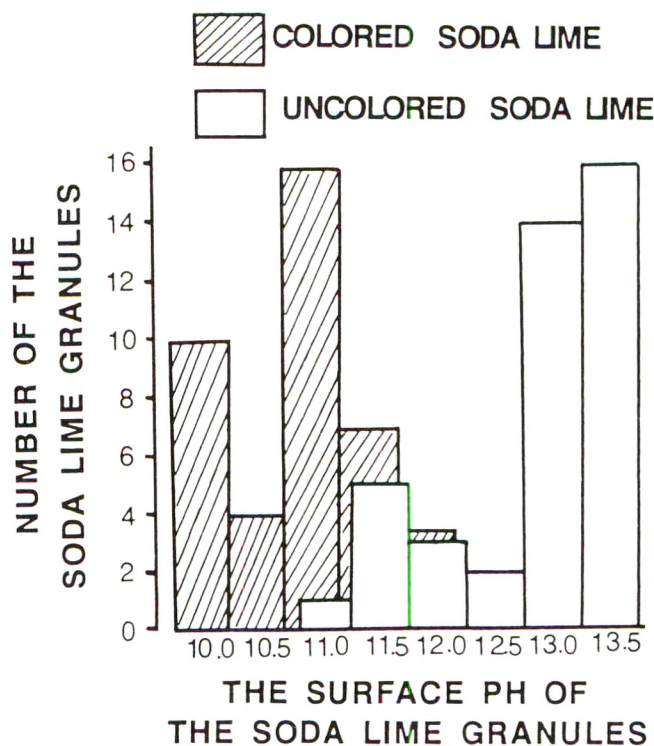
Figure 5. Number of the colored (N = 40) and uncolored (N = 40) granules of soda lime sampled from exhausted absorber is plotted against the surface pH of the soda lime granules. The surface pH of uncolored soda lime was significantly ($P < 0.005$) higher than that of the colored soda lime.

absorption of CO_2. In clinical situations, it is important to realize that even when the soda lime absorptive capacity has been exhausted, the pH will still be too high to change the indicator color.

We conclude that the dynamic and functional state of soda lime can be more precisely assessed by measuring changes in wall temperatures of the absorptive chambers than observing color changes. Thus, monitoring of changes in the temperature of the chambers of a divided canister is of clinical importance in order to maintain the patient's carbon-dioxide homeostasis during anesthesia. The time when the temperature of the second chamber exceeds that of the first should be employed as the clinical endpoint of the absorptive capacity of the first chamber. The first absorber should be discarded at this point and replaced by the second, with a new chamber containing fresh soda lime placed in the second chamber position.

References

1. Adriani J, Rovenstine EA. Experimental studies on carbon dioxide absorbers for anesthesia. Anesthesiology 1941;2:1–19.

2. Elam JO. Channeling and overpacking in carbon dioxide absorbers. Anesthesiology 1958;19:403–4.

3. Adriani J. Soda lime containing indicators. Anesthesiology 1944;5:45–52.

4. Orkin FK. Anesthetic systems. In: Miller RD, ed. Anesthesia 2nd ed. New York: Churchill Livingstone, 1986:117–60.

5. Linde HW. Anesthesia equipment. In: Dripps RD, Eckenhoff JE, Vandam L, eds. Introduction to Anesthesia 6th ed. Tokyo: WB Saunders, 1982:54–68.

6. Jorgensen B, Jorgensen S. The 600 gram CO_2 absorption canister. Acta Anaesthesiol Scand 1977;21:437–44.

7. Adriani J, Batten DH. The efficiency of mixtures of barium and calcium hydroxides in the absorption of carbon dioxide in breathing appliances. Anesthesiology 1942;3:1–10.

8. Lumley J, Morgan M. The temperature inside carbon dioxide absorbers. Anaesthesia 1976;31:63–8.

Clinical Reports

Autonomic Hyperreflexia in Spinal Cord Injured Patients during Extracorporeal Shock Wave Lithotripsy

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Extracorporeal shock wave lithotripsy (ESWL) is now widely used for treating kidney and ureteral stones as an alternative to percutaneous nephrolithotomy and surgical removal of stones (1). Patients with spinal cord injuries are quite prone to accumulate large stone burdens, especially staghorn calculi, which recur frequently and are difficult to pulverize with ESWL (2). Repeated shock waves normally elicit somatic and visceral pain. Patients with high spinal cord injuries, however, are left with motor and sensory loss below the level of the lesion and so do not generally require anesthesia for control of pain. But somatic and, particularly, visceral stimulation are well known to elicit reflex sympathetic vasoconstriction below the level of the lesion (3,4) which can trigger autonomic hyperreflexia (AHR) (5). AHR is known to occur frequently during bladder stimulation or urologic surgery in patients with spinal cord injuries above T_6 (6). The occurrence of AHR during ESWL has not been reported. The aim of our retrospective study was to examine if AHR occurs during ESWL in spinal cord injured patients given regional or general anesthesia.

Methods

The hospital records of all patients having ESWL during a 24-month period at our institution were examined retrospectively. Fifty-two patients (all male, age 48 ± 2 yrs) who had spinal cord injuries and underwent ESWL were identified and studied. All had complete spinal cord lesions resulting from trauma for at least five years. Each patient was given either general or regional anesthesia because of the possibility of developing AHR during ESWL. All patients received at least 500 ml of crystalloid intravenously before anesthesia and all were monitored noninvasively for ECG, blood pressure, and oxygen saturation by pulse oximetry. When general anesthesia was used, it was induced with thiopental followed by a non-depolarizing relaxant prior to intubation; maintenance of anesthesia was with nitrous oxide and either halothane or isoflurane in oxygen. Spinal and epidural anesthetics were administered in the lateral decubitus position using standard techniques at the L_3, L_4, or L_5 interspaces. Most patients having regional anesthesia were given supplemental oxygen by nasal cannula and in some blood pressure was monitored by radial arterial cannulation. In patients with high spinal cord lesions who were given intrathecal local anesthetics, the adequacy of anesthesia was assumed by a free flow of clear cerebrospinal fluid (CSF) with aspiration of CSF after injection of the anesthetic. In patients given spinal anesthesia with lidocaine (1–2 ml), 5% in $D_{7.5}W$ with 5 $\mu g/ml$ epinephrine was used. In patients given epidural anesthesia the loss of resistance test, with 1 ml of air or saline, was used to assess needle (17 g) placement in the epidural space; after epidural catheter placement, 3 ml of 2% lidocaine with 5 $\mu g/ml$ epinephrine

was used to assess inadvertent placement of the catheter in an epidural vein. The choice between spinal and epidural anesthesia was based arbitrarily on the expected difficulty of the anesthetic technique and the expected duration of ESWL. Urinary bladder catheterization and ureteroscopy, if performed, were done after anesthesia was induced. All patients were immersed in water for ESWL (Dornier HM3, Munich, West Germany). ESWL for spinal cord injured patients began 20 ± 2 SEM min after intrathecal or epidural injection and lasted 45 ± 5 min. AHR was defined as an unexpected and abrupt increase in blood pressure accompanied by an equally abrupt decrease in heart rate.

All values are expressed as means $\pm$ standard error of means (SEM). Maximal changes in blood pressure and heart rate after the onset of anesthesia and during AHR were compared to values obtained before anesthesia and were evaluated for statistical significance by two-way analysis of variance and comparison among means by LSD tests. Chi-squared tests (2 by 2 tables) were used to determine if the occurrence (frequency) of AHR in patients in whom AHR occurred was statistically significant compared with an equal number of patients in whom AHR is not expected to occur (zero frequency). A probability value of $P < 0.05$ was considered statistically significant.

Results

Three of the 52 spinal cord injured patients underwent ESWL three times and six underwent ESWL twice for a total of 64 ESWL procedures. The figure shows the distribution of spinal lesions in the 52 patients. Of the 64 anesthetics for ESWL, seven were general (three patients with lesions at C_3, and one each with lesions at C_5, T_7, T_9, and T_{12}), one was an epidural (lesion at T_3), and the remaining 56 anesthetics were spinal.

AHR did not recur in any patient who had more than one ESWL treatment. The average time between onset of anesthesia and end of ESWL in patients not exhibiting AHR was 60 ± 5 min. None of the five patients with lesions at C_3, three of whom had impaired breathing and were given general anesthesia and two of whom had spinal anesthesia, developed AHR. AHR developed once in 9 of the 52 patients during ESWL and began 73 ± 7 min after the onset of anesthesia (Fig. 1). Table 1 shows maximal changes in blood pressure and heart rate compared with preanesthetic controls in the 9 patients who developed AHR. Twenty-two of 23 patients with
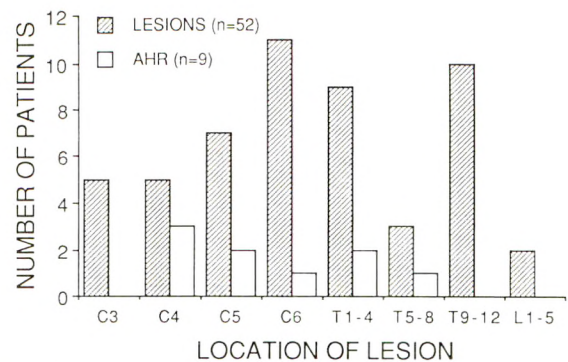
Figure 1. Number of patients with spinal cord lesions and those with AHR during ESWL. C, cervical; T, thoracic; L, lumbar; AHR, autonomic hyperreflexia.

Table 1. Blood Pressure and Heart Rate before and during Autonomic Hyperreflexia that Developed in 9 Patients

	BP (mm Hg)	HR (b/min)
Before anesthesia	$120 \pm 3/72 \pm 5$	73 ± 7
After anesthesia†	$96 \pm 9*/58 \pm 4$	82 ± 7
During AHR	$198 \pm 11*/112 \pm 6*$	$53 \pm 8*$

BP, systolic/diastolic blood pressure; HR, heart rate; after anesthesia, average of minimal BP, and maximal HR; AHR, maximal BP and minimal HR levels during autonomic hyperreflexia; all values are means $\pm$ SEM; *, $P < 0.05$ versus before anesthesia.

†Excludes one patient who had general anesthesia.

lesions at C_4, C_5, or C_6 had spinal anesthesia for ESWL; 6 of these 22, or 27%, had AHR. The observed frequency of AHR with ESWL in patients with cervical cord lesions was significantly greater ($P < 0.01$) than an expected frequency of 0% without ESWL. Of the 24 patients with thoracic or lumbar cord lesions, 3 of these, or 8%, experienced AHR; this frequency is not significant. Seven of the nine patients who developed AHR had no prior history of AHR, although all 9 had had prior surgery under general or spinal anesthesia.

In one patient (C_4) AHR occurred during ESWL 60 min after intrathecal injection of 15 mg of isobaric 0.75% bupivacaine. In five patients (C_{4-6}) AHR occurred during ESWL, 90, and 95 min after 100 mg of lidocaine; 45 min after 80 mg lidocaine; 75 min after 50 mg lidocaine; and 20 min after 50 mg lidocaine. In one patient (T_3), AHR occurred during ESWL 85 min following epidural administration of 280 mg lidocaine (2%). In another patient (T_4) AHR occurred 90 min after 100 mg lidocaine. In the final patient (T_7) AHR occurred during ESWL 20 min after induction of general anesthesia with nitrous oxide and isoflurane following a failed attempt at spinal anesthesia.

The hemodynamic changes of AHR appeared abruptly; in four of the 8 in whom AHR occurred during regional anesthesia, the onset of AHR was

accompanied by symptoms. One complained of chest pain, another complained of flank pain and two complained of headache. Hypertension, which lasted about 10–20 min, was treated intravenously in two patients with 10 mg hydralazine, in one patient with 20 mg nifedipine and sublingual nitroglycerin, and in another with 5 mg labetalol. Bradycardia was treated intravenously with atropine 0.4–1 mg in two of these patients with rapid correction of heart rate. Blood pressure and heart rate had returned approximately to pre-AHR levels on admission to the postanesthesia care unit. None of the patients required additional antihypertensive medications. No episodes of AHR occurred in the postanesthesia care unit within one hour after completion of ESWL.

Seven of the 28 patients with cervical cord lesions had a history of AHR but did not experience AHR with ESWL. Four of these patients had received 12–14 mg of tetracaine (1%) and ESWL ended 40, 60, 90, and 150 min after onset of spinal anesthesia. The fifth and sixth patient, respectively, had received 75 mg and 100 mg of lidocaine, and ESWL ended 70 and 80 min after the onset of spinal anesthesia. The seventh patient had general anesthesia with nitrous oxide and isoflurane and ESWL ended 80 min after induction. An additional patient with a T_3 lesion had a history of AHR but did not experience repeat AHR during ESWL.

Discussion

Extracorporeal shock wave lithotripsy (ESWL) is a nonsurgical method of pulverizing urinary tract stones by using focused shock waves (1). Anesthetic techniques employed to abolish the pain of ESWL include intercostal nerve blocks with local infiltration, general anesthesia, spinal or epidural local anesthesia (7–9), and more recently, epidural narcotics (10,11). With regional anesthesia a block between about T_5 and L_2 is adequate for pain relief (3).

AHR is a disorder of autonomic control of blood pressure (5) that can occur anytime after return of spinal cord reflexes following spinal cord injury. The incidence of AHR increases the more cephalad the cord lesion (5,6). Distention of a hollow viscus and surgery are potent stimuli for development of AHR (3–6,12). The neural pathway leading to AHR starts with afferent impulses which enter the cord below the lesion; these impulses trigger massive reflex sympathetic activity primarily over the splanchnic outflow tracts with resultant vasoconstriction and hypertension. Arterial baroreceptor stimulation leads appropriately to reflex bradycardia and vasodilatation above the cord lesion, but the sympathetic efferent impulses below the cord lesion are isolated from these reflexive inhibitory impulses so that vasoconstriction persists below the lesion. The end result is an increase in blood pressure and reflex bradycardia. Serious complications include cerebral, retinal, and subarachnoid hemorrhage, cardiac ischemia, and dysrhythmias (5,6,12).

AHR occurs in 65 to 85% of all patients with spinal cord injury above T_5 (5). The most frequent location of traumatic spinal cord lesions are: C_{4-7} (48%), T_{5-6} (13%) and T_{6-12} (18%) (6). Patients with spinal cord injury above T_7 may not need anesthesia for control of somatic and visceral pain below the level of the lesion. To prevent AHR, however, either general anesthesia, which blunts autonomic reflexes, or regional anesthesia, which blocks afferent and autonomic efferent neural impulses, is needed. Epidural, spinal, and general anesthesia have been employed to avoid development of AHR in spinal cord injured patients undergoing urologic procedures (3,4,12).

Schonwald et al. (4) found a 6% incidence of AHR in 100 spinal cord injured patients undergoing cystoscopy or transurethral sphincterotomy; in six patients mean blood pressure increased from 105/70 to 175/115 mm Hg and was accompanied by headache. Of these patients in whom AHR developed, two had spinal anesthesia with tetracaine, two had general anesthesia, one had topical anesthesia, and one had been given only intravenous sedation. However, AHR occurred only during recovery 3 to 3.5 hrs after the onset of spinal or general anesthesia. This suggests recovery from the effects of the regional or general anesthetic had occurred at the time of AHR.

The incidence of AHR in spinal cord injured patients undergoing ESWL has not been reported previously. One article (1) suggests that patients with spinal cord lesions do not require anesthesia for ESWL. Our review shows that although patients with spinal cord lesions had received general or regional anesthesia for ESWL to protect them from the potential for AHR and its complications, not all were protected from developing AHR. A significant number of patients (27%) with C_{4-6} cord lesions developed AHR during ESWL, even though they had spinal anesthesia. Since the level of autonomic, sensory, and motor blockade during regional anesthesia could not be evaluated before or during ESWL, patients who developed the characteristic signs of hypertension and bradycardia may have had a low, incomplete, or worn-off block. Of the 28 patients with cervical cord lesions, 7 had a history of AHR yet only two developed AHR with ESWL. For these patients in whom AHR did not occur, we assume that the

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general or spinal anesthetic was adequate to block or to attenuate the afferent or efferent autonomic nervous pathways and so prevent AHR during ESWL, or that ESWL did not trigger AHR.

Our major observations are that ESWL can indeed precipitate AHR in patients with spinal cord injuries and that AHR can develop during ESWL even though patients are given general or regional anesthesia. Our limited anesthetic experience with ESWL in spinal cord injured patients indicates that ESWL can cause, unpredictably, sufficient stimulation of somatic and/or visceral afferents in the area of the kidney to cause AHR in a significant number of patients. Because all spinal cord injured patients received either regional or general anesthesia for ESWL, we could not evaluate the effectiveness of anesthesia in preventing AHR. Suppression of autonomic spinal reflexes by either anesthetic method may protect against AHR during ESWL. We could not discern if general or regional anesthesia better protects against AHR with ESWL. For patients with high cervical cord lesions, we advise either sufficient general anesthesia or an adequate level of regional anesthesia to diminish the deleterious hemodynamic changes of AHR, should it occur during ESWL.

References

1. Lehman P, Weber W, Madler C, Schmitz E, Klaus P. In: Gravenstein JS, Klaus P, eds. Anesthesia and ESWL: five years of experience (Chapter 6), Extracorporeal Shock Wave Lithotripsy for Renal Stone Disease. Boston: Butterworths, 1986: 61–8.

2. Lazare JN, Saltzman B, Sotolongo J. Extracorporeal shock wave lithotripsy treatment of spinal cord injury patients. J Urol 1988;140:266–9.

3. Broecker BH, Hranowsky N, Hackler RH. Low spinal anesthesia for the prevention of autonomic dysreflexia in the spinal cord injury patient. J Urol 1979;122:366.

4. Schonwald G, Fish KJ, Perkash I. Cardiovascular complications during anesthesia and chronic spinal cord injured patients. Anesthesiology 1981;55:550–8.

5. Johnston B, Thomason R, Pallares V, Sadove MS. Autonomic hyperreflexia: a review. Milit Med 1975;140:345–9.

6. Kurnick NB. Autonomic hyperreflexia and its control in patients with spinal cord lesions. Ann Intern Med 1956;44:678–86.

7. Abbott MA, Samuel JR, Webb DR. Anaesthesia for extracorporeal shock wave lithotripsy. Anaesthesia 1985;40:1065–72.

8. Duvall JO, Griffith DP. Epidural anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1985;64:544–6.

9. Zeitlin GL, Roth RA. Effect of three anesthetic techniques on the success of extracorporeal shock wave lithotripsy in nephrolithiasis. Anesthesiology 1988;68:272–6.

10. Pandit SK, Powell RB, Crider B, McLaren IA, Rutter T. Epidural fentanyl: a simple and novel approach to anesthetic management for extracorporeal shock wave lithotripsy. Anesthesiology 1987;67:A225.

11. Madsen K, Ebert T, McDonald D, Eichner S, Stowe D. Comparison of epidural lidocaine and epidural narcotics for extracorporeal shock wave lithotripsy. Anesthesiology 1988;69:A403.

12. Lambert DH, Deane RS, Mazuzan JE jr. Anesthesia and the control of blood pressure in patients with spinal cord injury. Anesth Analg 1982;61:344–8.

Severe Reduction in End-Tidal PCO₂ following Unilateral Pulmonary Artery Occlusion in a Child with Pulmonary Hypertension

Evidence for Reflex Pulmonary Vasoconstriction

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Marked reductions in pulmonary blood flow decreases carbon dioxide elimination from the lung. Therefore monitoring of end-tidal P_{CO2} ($P_{ET}CO_2$) is particularly useful in patients with restricted pulmonary blood flow in whom pulmonary flow may be interrupted during surgery (1). Here we report our findings in a patient with pulmonary hypertension, related to an increased pulmonary blood flow, in whom a severe reduction in $P_{ET}CO_2$ occurred after occlusion of one pulmonary artery.

Report of a Case

A 4-month-old, 4.5 kg boy was admitted because of heart failure and cyanosis. His heart rate was 130 beats/min, respiratory rate was 60 breaths/min, and hematocrit was 0.52. A chest radiograph showed an enlarged heart and pulmonary congestion. Cardiac catheterization revealed a large ventricular septal defect, subaortic outflow tract obstruction, and severe pulmonary hypertension. Systemic venous blood was entering the aorta and pulmonary venous blood was entering the pulmonary artery. Sequentially measured pressures were 69/35 mm Hg in the aorta, 92/0 mm Hg in the left ventricle, 72/15 mm Hg in the right ventricle, and 85/27 mm Hg in the

pulmonary artery. An arterial blood sample obtained when the patient was breathing air had a pH of 7.38, a PCO_2 of 46 mm Hg, and a PO_2 of 37 mm Hg.

The child was scheduled for a Blalock-Hanlon procedure and banding of the pulmonary artery. He was premedicated with morphine 0.5 mg and atropine 0.1 mg subcutaneously. Anesthesia was induced with 60% nitrous oxide in oxygen and halothane. Pancuronium 0.5 mg was given for muscle relaxation and the trachea was intubated with a 4.0-mm uncuffed tube. After intubation the lungs of the patient were ventilated with 50% nitrous oxide in oxygen using an automatic ventilator with a minute volume of 3.5 l/min and a respiratory rate of 30 breaths/min. $P_{ET}CO_2$ was monitored with a Siemens Elema 930 CO_2 analyzer. A cannula was inserted in the right radial artery for monitoring arterial blood pressure. Fentanyl, 20 μg, was given IV before the start of surgery. A peripheral arterial blood sample obtained after skin incision had a pH of 7.36, a PCO_2 of 42 mm Hg, and a PO_2 of 49 mm Hg.

When the right pulmonary artery was occluded with a vascular snare prior to attempting the Blalock-Hanlon procedure there was an immediate, severe reduction in $P_{ET}CO_2$ and an increase in arterial blood pressure. The vascular snare on the right pulmonary artery was loosened, the trachea was suctioned and auscultation of the chest revealed normal bilateral breathing sounds. The FIO₂ was increased to 1.0. The right pulmonary artery was again occluded and again there was a severe decrease of $P_{ET}CO_2$ from 4.7 to 0.6% while arterial blood pressure increased initially from 58/44 to 89/55 mm Hg and slowly increased further to 97/75 mm Hg (Fig. 1). The vascular snare on the right pulmonary artery was loosened again. It was decided to perform banding of the mainstem of the pulmonary artery before proceeding to the Blalock-Hanlon procedure. After banding the pressure
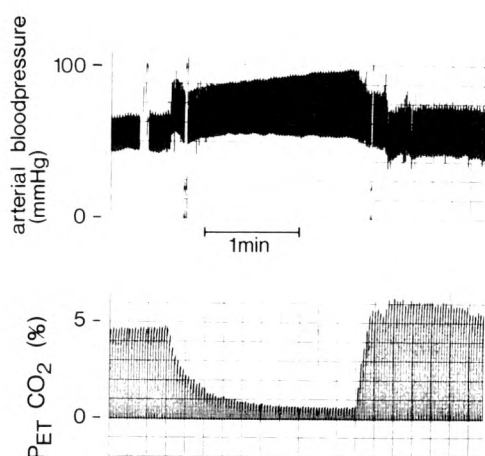
Figure 1. Arterial blood pressure and $P_{ET}CO_2$ during occlusion of the right pulmonary artery, before banding. At the first arrow the right pulmonary artery was occluded by a vascular snare. At the second arrow the vascular snare was released.
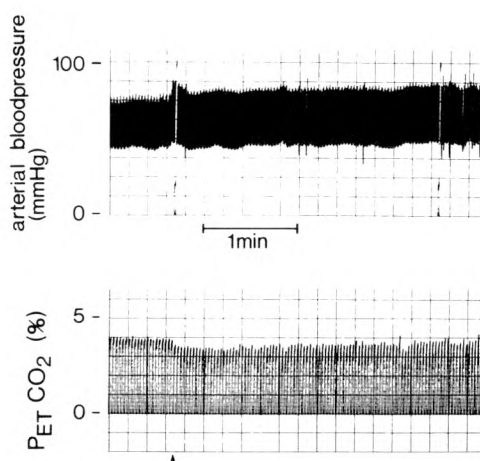
Figure 2. Arterial blood pressure and $P_{ET}CO_2$ during occlusion of the right pulmonary artery after banding. At the arrow the right pulmonary artery was occluded by a vascular snare.

in the pulmonary artery decreased to 36/18 mm Hg. The pressure in the radial artery was 67/43 mm Hg. Arterial blood pH was 7.38, PCO_2 38 mm Hg, and PO_2 45 mm Hg. When the right pulmonary artery was now occluded, $P_{ET}CO_2$ decreased only from 3.9 to 3.4% and arterial blood pressure increased from 75/48 to 84/48 mm Hg (Fig. 2). A Blalock-Hanlon procedure was performed. At the end of surgery, when FIO_2 was 0.5, pH was 7.40, PCO_2 34 mm Hg, and PO_2 48 mm Hg. Atropine 0.1 mg and neostigmine 0.3 mg were administered IV. Spontaneous ventilation started and the child was extubated. Postoperatively, the heart rate was initially 185 beats/min but decreased within 2 hours to between 138 and 148 beats/min after subcutaneous administration of morphine 0.5 mg. The respiratory frequency varied between 70 and 80 breaths/min. Furosemide 5 mg IV was admin-

istered. Postoperative fluids were administered at a rate of 10 ml/hour. Urine production was 10 ml/hour. Eleven hours after surgery poor peripheral circulation with peripheral cyanosis developed. Calcium gluconate, 100 mg, and dopamine up to 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were administered IV. Arterial blood pH was 7.36, PCO_2 41 mm Hg, and PO_2 48 mm Hg while receiving extra oxygen by a head box. A chest radiograph revealed an enlarged heart with clear lung fields. The child was transported to the operating room for debanding. Upon arrival heart rate suddenly decreased from 154 beats/min to 64 beats/min. The child was rapidly intubated, the thorax was opened and debanding was performed. Heart rate immediately returned to 158 beats/min. Forty-five minutes after debanding ventricular fibrillation developed. Resuscitation was unsuccessful. Autopsy revealed a criss-cross heart, atrioventricular concordance, a ventricular septal defect with a straddling left atrioventricular valve, upstairs-downstairs relation of the ventricles, a double outlet right ventricle, and a subvalvular aortic stenosis.

Discussion

In patients without cardiopulmonary disease occlusion of one pulmonary artery causes minimal changes in $P_{ET}CO_2$ provided the ventilation to the contralateral lung is normal. In our patient the decrease in $P_{ET}CO_2$ after occlusion of the right pulmonary artery is unlikely to have been due to inadequate ventilation of the left lung. On auscultation bilateral breathing sounds were present. Also occlusion of the right pulmonary artery after banding caused only minimal changes in $P_{ET}CO_2$.

When one pulmonary artery is occluded the cardiac output has to be accommodated by the nonoccluded lung. In humans without cardiopulmonary disease this increased flow does not result in a major increase in pulmonary artery pressure since the nonoccluded lung decreases its vascular resistance (2). The decrease in pulmonary vascular resistance is due to a combination of vascular dilatation and recruitment of previously nonperfused vessels. For patients with severe pulmonary hypertension the ability to decrease vascular resistance by distension and/or recruitment may be limited. In these patients clamping of one pulmonary artery will result in a marked increase in pulmonary arterial pressure, but flow through the other lung will be maintained. However the severity of the decrease in $P_{ET}CO_2$ in our patient from 4.7 to 0.6%, indicates almost complete cessation of blood flow to the left lung.

In dogs pressor receptors have been located in the vicinity of the bifurcation of the pulmonary artery (3). In animals without pulmonary hypertension distension of a pulmonary artery in the region of the bifurcation results in an increase in distal pulmonary artery pressure which was attributed to reflex pulmonary vasoconstriction (4-6). Clamping of a pulmonary artery does not result in reflex pulmonary vasoconstriction (7). Reflex pulmonary vasoconstriction is only seen when the pulmonary artery is distended in the region of the bifurcation. In lambs the pulmonary vasoconstrictive reflex decreases during the first months of life (8). There is evidence that this reflex is also present in human infants (9). Reflex pulmonary vasoconstriction is thought to be important in maintaining a high pulmonary vascular resistance during fetal life, promoting blood flow through the ductus arteriosus from the pulmonary artery into the aorta (8).

The existence of a pulmonary vasoconstrictive reflex has been questioned (10,11). Constriction of pulmonary vessels following distension of the pulmonary artery has never been demonstrated, only increases in pulmonary artery pressure. We did not monitor pulmonary arterial pressure in our patient during the period of right pulmonary artery occlusion. However, in our opinion, the findings in our patient provide further evidence for the presence of a pulmonary vasoconstrictive reflex in human infants. With occlusion of the right pulmonary artery the total pulmonary blood flow had to be accommodated by the left pulmonary artery. Because of the existing pulmonary vascular disease this would have resulted in a further increase in pressure in the pulmonary artery and distension of the pulmonary artery with activation of the reflex. The resulting pulmonary vasoconstriction led to a marked decrease in blood flow to the left lung and thus the fall in $P_{ET}CO_2$. Because of the presence of a ventricular septal defect blood flow was redirected into the aorta increasing arterial blood pressure.

In summary, while demonstrating the value of monitoring $P_{ET}CO_2$ in a patient with pulmonary hypertension in whom occlusion of the right pulmonary artery was surgically attempted we report evidence suggesting activation of a pulmonary vasoconstrictive reflex secondary to pulmonary artery distension.

References

1. Schuller JL, Bovill JG, Nijveld A. End-tidal carbon dioxide concentration as an indicator of pulmonary blood flow during closed heart surgery in children. A report of two cases. Br J Anaesth 1985;57:1257-9.

2. Charms BL. Unilateral pulmonary artery occlusion. In: Zimmerman HA. Intravascular catheterization. Springfield: Charles C Thomas, 1966:942-1010.

3. Coleridge JCG, Kidd C. Electrophysiological evidence of baroreceptors in the pulmonary artery of the dog. J Physiol 1960;150:319-33.

4. Aramendia P, Taquini CM, Fourcade A, Taquini AC. Reflex vasomotor activity during unilateral occlusion of the pulmonary artery. Am Heart J 1963;66:53-60.

5. Juratsch CE, Grover RF, Rose CE, Reeves JT, Walby WF, Laks MM. Reversal of reflex pulmonary vasoconstriction induced by main pulmonary artery distension. J Appl Physiol 1985;58: 1107-14.

6. Hyman AL. Pulmonary vasoconstriction due to nonocclusive distension of large pulmonary arteries in the dog. Circ Res 1968;23:401-13.

7. Osorio J, Russek M. Reflex changes on the pulmonary and systemic pressures elicited by stimulation of baroreceptors in the pulmonary artery. Circ Res 1962;10:664-7.

8. Juratsch CE, Emmanouilides GC, Thibault DW, Baylen BG, Jengo JJ, Kaks MM. Pulmonary arterial hypertension induced by distension of the main pulmonary artery in conscious newborn, young and adult sheep. Pediatr Res 1980;14:1332-8.

9. Baylen BG, Emmanouilides GC, Juratsch CE, Yoshida Y, French WJ, Criley JM. Main pulmonary artery distension: a potential mechanism for acute pulmonary hypertension in the human infant. J Ped 1980;96:540-4.

10. Lloyd TC Jr. Pulmonary arterial distension does not cause pulmonary vasoconstriction. J Appl Physiol 1986;61:741-5.

11. Lloyd TC Jr, Juratsch CE. Pulmonary hypertension induced with an intra-arterial balloon: an alternate mechanism. J Appl Physiol 1986;61:746-51.

Malignant Hyperthermia-Like Syndrome Associated with Metrizamide Myelography

Robert O. Ong, MD, and Henry Rosenberg, MD

Malignant hyperthermia (MH) is a potentially fatal syndrome occurring during or after anesthesia conducted with potent inhalation anesthetics agents and/or succinylcholine (1). Fever is the most distinctive sign and is usually accompanied by severe acidosis, tachycardia, tachypnea, and muscle rigidity.

We report a case of a life threatening reaction to an intrathecal injection of metrizamide (Amipaque), a nonionic, iodinated, water-soluble contrast media, after anesthesia conducted with MH triggering anesthetics. Because fever, acidosis, and muscle hypertonicity suggested a diagnosis of MH, dantrolene therapy was instituted. However, subsequent muscle biopsy and testing with halothane and caffeine failed to substantiate the diagnosis.

With increased suspicion of MH, it is important to recognize that not all postoperative fevers are caused by MH and that successful management requires a careful consideration of other possibilities after initial treatment of suspected MH proves unresponsive to therapy.

Case Report

D.E.H. was a 25-year-old, 114-kg man initially admitted to another hospital for elective laminectomy and discectomy after a history of severe post-traumatic back and leg pain. Past medical history was unremarkable except that the patient had repair of a testicular torsion at age 6 years without problems (anesthetics unknown). There was no family history

of anesthesia-related problems. Preoperatively, the patient appeared to be in good health.

Admission laboratory findings included hemoglobin 15.3 g%, sodium 142 mEq/liter, potassium 4.1 mEq/liter, and CPK 202 IU/liter (normal limits 37–289 IU/liter). Urinalysis and chest X-ray were within normal limits. The patient was premedicated with glycopyrrolate 0.2 mg, meperidine 75 mg, and promethazine 2.5 mg intramuscularly. After anesthesia was induced with thiopental 400 mg, succinylcholine 100 mg IV was administered, and the patient was intubated and turned to the prone position. No problems were encountered during intubation. Anesthesia was maintained with isoflurane plus nitrous oxide in oxygen. Relaxation was provided with atracurium 50 mg IV in divided doses as indicated by the response to ulnar nerve stimulation. The procedure lasted 3.5 hours. There was no muscle rigidity or fever. During surgery, a myelogram of the lumbar region was performed with 10 ml of metrizamide contrast media at a concentration of 200 mg/ml iodine. At the end of the procedure, the patient's residual muscle paralysis was reversed with neostigmine 3 mg and glycopyrrolate 0.6 mg, and his trachea was extubated without any problems.

One hour after arriving in the recovery room, the patient had the onset of generalized itching. His heart rate was 165 beats/minute. He was given meperidine 25 mg IV, midazolam 2 mg IV, and propranolol 0.5 mg IV. At this time, his rectal temperature was 101.9°F (38.8°C). Within the next hour, the patient began having periodic jerks of his arms and legs every 3–5 minutes, lasting 1–2 minutes. An arterial blood sample showed mild acidosis with pH 7.29, pO_2 115 mm Hg, and pCO_2 47 mm Hg, HCO_3^- 26 mEq/liter.

The presumptive diagnosis of malignant hyperthermia was made, and the patient was given dantrolene 2 mg/kg IV. However, his temperature rose to 102°F (39°C) over the next hour. Arterial blood gas data included pH 7.15, pO_2 72 mm Hg, pCO_2 65 mm Hg, HCO_3 28 mEq/liter at that time. A second dose of

dantrolene 1 mg/kg of body weight IV with intravenous normal saline solution plus 2 mg/kg of furosemide, 1.5 gm/kg of mannitol, and 1 mEq/kg of bicarbonate were given without significant improvement. Eventually, because of a seizure and later cyanosis, he was reintubated and given supplemental oxygen and mechanically ventilated with FIO_2 1.0 tidal volume 1000 ml, ventilatory rate of 20/minute and PEEP 10 cm H_2O. Another arterial blood gas sample revealed a pH of 6.97, pO_2 37 mm Hg, pCO_2 101 mm Hg. There was evidence of pulmonary edema on chest X-ray film. Serum creatinine phosphokinase (CPK) level increased to over 4000 IU/liter 3 hours after the surgery, and the urine was pink-tinged, presumably indicative of myoglobinuria. Tests for myoglobinemia were not performed.

With further symptomatic treatment including phenytoin 1 gm IV for control of seizures and respiratory support, the patient's fever resolved, breathing function returned to normal, and within 48 hours mechanical ventilation was discontinued. His recovery thereafter was uneventful.

Because of the suspicious nature of the episode, especially the unexplained fever occurring after an anesthetic with agents known to be MH triggers, the patient was referred to us for a diagnostic muscle biopsy 3 months later. Testing of the biopsied vastus lateralis muscle with halothane and caffeine (1) revealed a completely normal response (maximum contracture to 3% halothane of 0.4 g and no contracture to 2 mM caffeine).

Discussion

The differential diagnosis of fever after anesthesia includes infection, allergy, drug reaction, MH, and an alteration of metabolism as may occur with thyroid storm. Because of the use of two well-known MH triggering agents in the present case (succinylcholine and isoflurane) and development of tachycardia, flushing, hyperventilation, acidosis, rhabdomyolysis, possible myoglobinuria and elevated CPK, a diagnosis of MH was made.

However, the failure of a prompt response to dantrolene and the peculiar seizure-like activity were atypical for MH. There was no clinical evidence of thyroid disorder, pheochromocytoma, or infection that might account for the postoperative events this patient experienced.

Metrizamide (Amipaque) is a nonionic, water-soluble contrast agent widely used for myelography. Its specific gravity ranges from 1.184 at 170 mgI/ml to 1.329 at 300 mgI/ml (CSF normal range is 1.005 to 1.009). Although it is a hyperbaric contrast agent, metrizamide diffuses or is actively transported slowly cephalad through the cerebrospinal fluid (CSF) after subarachnoid placement, irrespective of the position in which the patient is maintained. After lumbar injection in a semi-sitting position, for example, small concentrations can be demonstrated in the posterior fossa after 6 hours and over the cerebral convexities after 24 hours (2). Most common side effects, e.g., headache (58%), nausea and vomiting (70%), dizziness (18%), and mental confusion (8%), reach a peak several hours after injection (3). Seizures are rare, and temperature elevation is most common in patients under 18 years old (4). Metrizamide may also be associated not only with fever but also with spinal hyperactivity in the form of prolonged myoclonic spasms of the trunk and lower extremities. This was first documented by Paling et al. (5–8). Animal studies (9–13) demonstrated that muscle hypertonicity and spasm occurred a few hours after dye injection. Presumably, the reason for delayed onset is the time necessary for the dye to ascend into the basal cisterns (7,8). Because in this case the myelogram was performed with the patient in the prone position with the back flat but head down, it is conceivable that the dye ran up from the low back to the head. If a patient is tilted head down, a higher intracranial concentration is achieved and more cerebral side effects may be expected (14,15).

Metrizamide diffuses readily across the pia mater or ependyma into subjacent brain (16,17). The probability of intrathecal metrizamide side effects is not only dose-related but also site-dependent (14). Cortical penetration and probably severe reactions with metrizamide are, however, rare with total doses less than 1.6 g given intrathecally. Most neurotoxic effects probably occur by a direct effect of metrizamide on central nervous system (CNS) function. Bertoni (18,19) demonstrated that metrizamide competitively inhibits brain hexokinase, probably because its glucosamine moeity acts as a glucose analog (20). Another possible mechanism of CNS toxicity is an inhibition of acetylcholinesterase activity (21).

In summary, to the list of the many possible etiologies of temperature elevation after surgery, we can add yet another: reaction to radiologic contrast material injected into the subarachnoid space. The case reported here illustrates that not all postoperative fevers represent MH. In situations in which the diagnosis of MH is suspected but the signs of MH are atypical or the response to dantrolene unusual, follow-up muscle biopsy utilizing halothane and caffeine contracture test protocol is advised.

References

1. Rosenberg H. Clinical presentations of malignant hyperthermia. Br J Anaesth 1988;60:268–73.

2. Hindmarsh T. Elimination of water-soluble contrast made from the subarachnoid space: investigations with CT. Acta Radiol (suppl) 1975;346:45–50.

3. Yu Y, du Boulay GH, Paul E. Influence of certain factors on the manifestations of the adverse effects of metrizamide myelography. Neuroradiology 1986;28:339–43.

4. Product Information: Metrizamide (Amipaque). Winthrop Laboratories, 90 Park Ave., NY, NY 10016.

5. Paling MR, Quindlen EA, DiChiro G. Spinal Seizures after metrizamide myelography in a patient with a spinal block. Am J Radiol 1980;135:1091–2.

6. Skalpe IO. The toxicity of non-ionic, water-soluble monomeric/dimeric contrast media in selective vertebral angiography. Neuroradiology 1983;24:219–23.

7. Russel D, Anke IM, Nyberg-Hansen R, Slettness O, Sortland O, Veger T. Complex partial status epilepticus following myelography with metrizamide. Ann Neurol 1980;8:325–7.

8. Shiozawa Z, Sasaki H, Ozaki Y, Nakanishi T, Huang YP. Epilepsis partialis continua following metrizamide cisternography. Ann Neurol 1981;10:400–1.

9. Block BP, Ginocchio AV. Local and systemic subarachnoid toxicity of metrizamide in mice and monkeys. Acta Radiol (suppl) 1973;335:14–24.

10. Oftedal SI. Toxicity of water-soluble contrast media injected suboccipitally in cats. Acta Radiol (suppl) 1973;335:84–92.

11. Oftedal SI, Kayed K. Epileptogenic effect of water-soluble contrast media: an experimental investigation in rabbits. Acta Radiol (suppl) 1973;335:45–56.

12. Skalpe IO, Torvik A. Toxicity of metrizamide and meglumine iocarmate after suboccipital injection in rats. Invest Radiol 1975;10:154–9.

13. Skalpe IO, Aulie A. The toxicity of non-ionic, water-soluble contrast media in selective vertebral angiography: an experimental study in rabbits with special reference to the difference between monomeric and dimeric compounds. Neuroradiology 1985;27:77–9.

14. Gulati AN, Guadagnoli DA, Quigley JM. Relationship of side effects to patient position during and after metrizamide lumbar myelography. Radiology 1981;141:113–6.

15. Robertson WD, Lapointe JS, Nugent RA, Robinson RG, Daly LF. Positioning of patients after lumbar myelography. Am J Radiol 1980;134:947–8.

16. Drayer BP, Rosenbaum AE. Metrizamide brain penetrance. Acta Radiol (suppl) 1977;355:280–93.

17. Fenstermacher JD, Bradbury MWB, du Boulay G, Kendall BE, Rader EW. The distribution of ^{125}I metrizamide and ^{125}I diatrizoate between blood, brain and cerebrospinal fluid in the rabbit. Neuroradiology 1981;19:171–90.

18. Bertoni JM. Metrizamide inhibiting human brain hexokinase. Neurology 1982;32:884–7.

19. Bertoni JM, Schwartzmann RJ, Van Horn G, Partin J. Asterixis and encephalopathy following metrizamide myelography: investigations into possible mechanisms and review of the literature. Ann Neurol 1981;9:366–70.

20. Junck L, Marshall WH. Neurotoxicity of radiologic contrast agents. Ann Neurol 1983;13:469–84.

21. Marder E, O'Neil M, Grossman RI, David KR, Taveras JM. Cholinergic action of metrizamide. Am J Neuroradiol 1983;4:61–5.

Dose-Response Study of Droperidol and Metoclopramide as Antiemetics for Outpatient Anesthesia

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Key Words: ANESTHESIA, OUTPATIENT. VOMITING, ANTIEMETICS—droperidol. ANESTHETICS, INTRAVENOUS—droperidol. GASTROINTESTINAL TRACT, STOMACH—metoclopramide.

During the past decade the demand for outpatient surgery has grown rapidly. To keep pace with the changing surgical environment, anesthesiologists have been modifying their anesthetic techniques to ensure a more rapid and a smoother recovery. However, postoperative nausea and vomiting remain the most common anesthesia-related side effects in outpatient surgical facilities (1,2). The incidence of postoperative nausea and vomiting in female outpatients undergoing laparoscopy has been reported to be as high as 50–60% (3). The incidences after strabismus surgery (4) and after therapeutic abortions (5) are also high. A prophylactic antiemetic would be of great value in outpatient surgery and anesthesia.

A large number of papers have been published suggesting the use of droperidol, a butyrophenone derivative, as a prophylactic antiemetic agent. Although the majority of the authors found droperidol to be an effective antiemetic, the recommended doses vary widely (4,6–8). However, side effects, especially somnolence, have been reported with larger doses (4,9). Metoclopramide, a dopaminergic receptor blocker devoid of sedative effects, has also been advocated as an antiemetic, but conflicting results have been reported regarding its efficacy (5,10–14). A recent paper by Rao, et al. (15) reported no nausea or

vomiting at all after oral metoclopramide (10 mg) in female patients undergoing a laparoscopy, thus raising many expectations among the anesthesiologists practicing outpatient anesthesia.

Because of these conflicting results and because the efficacy of a combination of droperidol and metoclopramide has not been evaluated we carried out a double blind and randomized controlled dose-response study with three different intravenous doses of droperidol, two standard doses of oral metoclopramide, and a combination of the two agents in adult females undergoing outpatient laparoscopy under general anesthesia.

Methods

The institutional ethical committee at this medical center approved the study, and each patient gave written consent to participate. One hundred and forty adult females, ASA physical status 1 or 2, scheduled for an outpatient laparoscopy participated in this study. The antiemetic agents were dispensed in a randomized double-blind fashion (see Table 1). Each patient received both a pill (either a lactose placebo or metoclopramide) and an intravenous injection (saline placebo or droperidol). The oral agents were given about 30 min prior to induction of anesthesia and the intravenous agents were administered 2 min prior to induction. A nurse not involved in any of the subsequent evaluations, dispensed and administered the medications following a computer-generated random list. There were seven groups with 20 patients in each group.

The anesthetic regimen was standard for all patients. Each patient was pretreated with fentanyl 1 μg/kg 2 min prior to induction of anesthesia with thiamylal 4 mg/kg. Vecuronium 0.1 mg/kg was used to facilitate tracheal intubation. Anesthesia was maintained with gradually decreasing concentrations of enflurane (2.5% to 0.5%) in nitrous oxide and oxygen

Table 1. Medications Received by Patients in
Different Groups

Group	N	Oral medication	Intravenous medication
1	20	Metoclopramide 5 mg	Placebo
2	20	Metoclopramide 10 mg	Placebo
3	20	Placebo	Droperidol 5 μg/kg
4	20	Placebo	Droperidol 10 μg/kg
5	20	Placebo	Droperidol 20 μg/kg
6	20	Placebo	Placebo
7	20	Metoclopramide 10 mg	Droperidol 10 μg/kg

(2:1 l/m). Additional vecuronium was used if necessary, but additional narcotics were avoided. The enflurane was turned off when the surgeon started to close the wound and the nitrous oxide was turned off when the skin suturing was completed. The effect of the muscle relaxant was reversed with neostigmine and glycopyrrolate when the surgical dressings were applied.

Postanesthetic care and observations were also standardized. The same blinded observer (SPK) performed all the assessments in the recovery room and conducted telephone follow-up after 24 hours. All recovery times (described below) were measured from the time that nitrous oxide was discontinued. The time to complete orientation (ability to correctly tell day, date, and date of birth) and the time before the patient was able to walk to the bathroom were recorded. Patients were discharged following preset clinical criteria (16) (stable blood pressure, pulse rate, and respiratory rate, absence of respiratory problems, presence of gag reflex, ability to ambulate, ability to void, ability to tolerate oral fluid) and the time to discharge was noted.

Patients complaining of severe pain in the recovery room were given fentanyl 25 ug IV which was repeated once or twice if necessary. If patients could tolerate oral medication, ibuprofen 400–600 mg was given for pain. All patients were discharged with a prescription for oral ibuprofen to be taken if necessary. In cases of excessive nausea and vomiting, prochlorperazine 5 mg IV was used. If more than one dose of antiemetic was required, the subsequent medications were either same dose of prochlorperazine or droperidol 0.6 mg IV.

The frequency of nausea and vomiting was assessed by direct questioning every 15 min in the recovery room and by telephone 24 hours after the operation. The frequency was recorded in 3 categories: no nausea or vomiting or retching; nausea only; both nausea and either vomiting or retching. The severity of the symptoms was further recorded on the basis of additional antiemetic therapy required in the

recovery room (none, one dose, or more than one dose).

One way analysis of variance (ANOVA) was used for parametric data analysis. To compare the incidence of nausea/vomiting between the placebo group and the other groups, a chi-square test was used for nonparametric analysis.

Results

The seven groups (N = 20) were comparable with regard to age, weight, height, duration of anesthesia, and use of fentanyl in the recovery room. The average duration of anesthesia was 70 minutes (Table 2).

The incidence of nausea and vomiting in the seven groups is shown in Table 3. Patients in group 6, who received an oral placebo as well as an intravenous placebo, had the greatest frequency of nausea and vomiting (65%). Twenty-five percent had nausea only and 40 percent had both nausea and vomiting. Only groups 4 (placebo plus droperidol 10 μg/kg), group 5 (placebo plus droperidol 20 μg/kg), and group 7 (metoclopramide 10 mg plus droperidol 10 μg/kg) were significantly different than the group 6 (placebo plus placebo). Groups 1, 2, and 3, which received either oral metoclopramide (and placebo intravenously) or a small dose of droperidol 5 μg/kg IV (and oral placebo), were not significantly different from group 6 (placebo plus placebo). In other words, only in the groups that received at least 10 μg/kg of droperidol (with or without oral metoclopramide) was there a significant reduction in the incidence of nausea and vomiting compared to the group receiving placebos.

The incidence of patients requiring additional doses of antiemetics in the recovery room is shown in Table 4. The only group that needed no additional antiemetic in the recovery room was group 5, which received oral placebo plus droperidol 20 μg/kg IV prophylactically. This was also the only group which was statistically different from group 6 (placebo plus placebo) in this regard. In addition, although the results were not statistically significant, it is important to note that none of the patients who received at least some droperidol as prophylactic treatment (5, 10, or 20 μg/kg) needed more than one additional treatment. This was not true for patients receiving only metoclopramide or placebo.

Times to orientation, ambulation, and discharge are shown in Table 5. ANOVA analysis showed no significant difference among the groups. However, there was a trend toward faster recovery in patients who received metoclopramide.

Table 2. Demographic Parameters and Duration of Anesthesia in Seven Groups

Groups	Age (yrs) mean ± SD	Height (cm) mean ± SD	Weight (lbs) mean ± SD	Duration of anesthesia (min) mean ± SD
Metoclopramide 5 mg plus placebo	30.3 ±(6.59)	64.3 ±(2.31)	139.2 ±(32.87)	68.0 ±(17.8)
Metoclopramide 10 mg plus placebo	31.1 ±(7.11)	63.6 ±(1.67)	144.1 ±(28.38)	67.0 ±(14.64)
Placebo plus droperidol 5 µg/kg	30.0 ±(7.24)	63.9 ±(2.70)	139.1 ±(34.50)	69.8 ±(19.09)
Placebo plus droperidol 10 µg/kg	30.3 ±(5.65)	64.5 ±(2.37)	132.6 ±(20.91)	71.5 ±(20.47)
Placebo plus droperidol 2 0 µg/kg	29.0 ±(5.68)	64.8 ±(2.65)	137.6 ±(27.86)	65.1 ±(15.14)
Placebo plus placebo	31.5 ±(4.49)	64.0 ±(3.02)	139.7 ±(34.74)	64.8 ±(22.97)
Metoclorpramide 10 mg plus droperidol 10 µg/kg	29.0 ±6.51	64.4 ±2.28	143.1 ±21.05	65.0 ±17.62

ANOVA analysis show no difference among the groups.

Table 3. Frequency of Nausea and Vomiting (as percentage of 20 patients in each group) in the Recovery Room

Groups	No nausea or vomiting (%)	Nausea only (%)	Nausea and vomiting (%)	Any nausea/ vomiting (%)
Meto 5 mg plus placebo	45	30	25	55
Meto 10 mg plus placebo	55	25	20	45
Placebo plus Drop 5 µg/kg	60	20	20	40
Placebo plus Drop 10 µg/kg	75	20	5	25*
Placebo plus Drop 20 µg/kg	80	10	10	20*
Placebo plus placebo	35	25	40	65
Meto 10 mg plus Drop 10 µg/kg	75	20	5	25*

Chi-square tests were performed with raw numbers (percentage of total shown in the table).
*P < 0.05 (Group 6 placebo plus placebo significantly different from group 4 (droperidol 10 µg/kg), group 5 (droperidol 20 µg/kg), and group 7 (metoclopramide 10 mg plus droperidol 10 µg/kg).

Table 4. Percentage of Patients Requiring Additional Antiemetic Therapy in the Recovery Room

Groups	No additional treatment (%)	One additional treatment (%)	Two or more additional treatment (%)
Metoclopramide 5 mg	70	25	5
Metoclopramide 10 mg	75	10	15
Droperidol 5 µg/kg	90	10	0
Droperidol 10 µg/kg	85	15	0
Droperidol 20 µg/kg	100*	0	0
Placebo	60	35	5
Metoclopramide 10mg plus droperidol 10 µg/kg	90	10	0

Chi-square tests were performed with raw data. Only group 5 (droperidol 20 µg/kg) was significantly different from placebo (group 6).
*P < 0.05.

Table 6 shows the discharge times of all patients, grouped according to whether or not they were nauseated and/or vomited in the recovery room. Irrespective of antiemetic therapy received, the presence of nausea and vomiting significantly increased discharge times.

The incidence of nausea and vomiting during transit from the hospital to residence and also at home was low (5–10%), and there were no significant differences between the groups. Most patients (85–

90%) felt normal by the day after the operation. There were no cases of protracted nausea and vomiting that needed either hospital admission or further antiemetic therapy at home.

Discussion

The results of our study confirmed that droperidol, a butyrophenone derivative given at the time of induction of anesthesia in appropriate doses, is an effective antiemetic in female patients undergoing outpatient

Table 5. Times to Orientation, Ambulation and Discharge (minutes, mean ± SD)

Groups	Orientation	Ambulation	Discharge
Metoclopramide 5 mg	16.7 ± 6.50	128.5 ± 35.88	169.5 ± 60.82
Metoclopramide 10 mg	17.2 ± 5.00	124.5 ± 39.00	167.3 ± 62.86
Droperidol 5 μg/kg	18.3 ± 5.20	146.5 ± 42.50	185.3 ± 37.01
Droperidol 10 μg/kg	18.7 ± 6.95	149.8 ± 55.12	189.8 ± 73.55
Droperidol 20 μg/kg	17.0 ± 6.96	142.3 ± 45.52	179.5 ± 43.04
Placebo	15.3 ± 5.25	150.3 ± 48.44	202.0 ± 68.72
Combination	17.9 ± 5.74	134.8 ± 38.64	197.0 ± 83.45

ANOVA showed no difference among groups.

Table 6. Discharge Time for All Patients With or Without Nausea/Vomiting

Symptom	N	Time to discharge minute (mean ± SD)
No nausea/vomiting	85	165.9 ± 47.02
Nausea only	30	196.8 ± 54.86*
Nausea and vomiting	25	231.8 ± 88.82**

ANOVA showed significant difference ($P < 0.05$) between the groups.
*$P < 0.05$ versus no nausea/vomiting.
**$P < 0.0001$ versus no nausea/vomiting.

laparoscopy. Metoclopramide, on the other hand, when given orally at a standard (5 or 10 mg) dose 30 minutes before induction of anesthesia, was no different than a placebo as an antiemetic agent. The results of this prospective randomized study should clear up much of the existing confusion regarding both the appropriate dose of droperidol as an antiemetic as well as the lack of effectiveness of metoclopramide as an antiemetic.

Droperidol had been reported to be effective in doses as small as 0.25 mg (Shelley ES and Brown HA: Antiemetic effect of ultra low dose droperidol. ASA Annual Meeting abstract, 1978) and 5 μg/kg (6), and as large as 2.5 to 5 mg (4,8,17,18), although a proper dose-response study in a standard patient population had not been done previously. We found the lower dose of 5 μg/kg (approximately 0.3 mg in a 70-kg person) to be unreliable as an antiemetic, but both 10 and 20 μg/kg (approximately 0.625 mg and 1.25 mg for a 70-kg person) respectively were more effective than a placebo. The 20-μg/kg prophylactic dose not only reduced the incidence of nausea and vomiting in these patients but also eliminated the need for additional antiemetic agents during recovery in those few patients who still felt nauseated. Thus, 20 μg/kg droperidol was able to reduce both the frequency as well as severity of the symptoms.

Droperidol is not devoid of side effects. Extrapyramidal symptoms (19) as well as bizarre psychosis (20,21) have been reported following premedication with droperidol. We made it a point to administer droperidol immediately prior to induction of anesthesia to avoid those possible side effects. The other reported side effect of droperidol is prolonged postoperative sedation. This side effect has been reported only after the use of larger doses of droperidol, 2.5 mg or higher (4,9). We found that a modest dose (1.25 mg per 70 kg) of droperidol was not only an effective antiemetic but did not cause excessive sedation in the postoperative period nor did it prolong discharge times. Our findings in this respect are similar to those of Korttila, et al. (7) and Wetchler, et al. (Wetchler BV, Collins IS, Jacob L: Antiemetic effects of droperidol on the ambulatory surgery patient. Anesthesiology Review, 1982;9:23-26).

Conflicting results have been reported in the literature regarding the efficacy of metoclopramide as an antiemetic agent. Review of these data shows an interesting trend. In general, metoclopramide given intravenously (5,7,13,14) was ineffective, but given either intramuscularly (10,12) or orally (15) it appeared effective as an antiemetic. This might indicate a difference in the bioavailability of the drug in the immediate postoperative period. However, even with two different oral doses, we could not reproduce the results of Rao, et al. (15), who found a 0% incidence of nausea and vomiting after oral metoclopramide. The patients in the study of Rao, et al. received their oral metoclopramide (10 mg) at home before coming to the hospital for the operation. Our patients were given the drug in the preanesthetic holding room 30 minutes prior to induction of anesthesia. This difference in time of drug administration can not explain the different results we have found. Pharmacokinetic studies (22) with oral metoclopramide demonstrated that maximum plasma concentration after oral administration occurs within 20-30 minutes and its elimination half life is about 4-5 hours.

We noticed an interesting trend toward quicker recovery in patients receiving metoclopramide. Although this was not statistically significant, we mention it because Cohen, et al. (5) noticed similar trends earlier.

Doze, et al. (2) recently found a combination of droperidol and metoclopramide to be a more effective antiemetic than either drug given alone before general anesthesia for an abortion. Our results differed in that we found no advantage of this combination in patients undergoing laparoscopy. Doze, et al. used

no placebo control and their patients received three different anesthetic regimens.

We confirmed the observations made by others (1,2) that the occurrence of nausea and vomiting significantly prolongs recovery room stay irrespective of antiemetic therapy.

We conclude that droperidol is an effective antiemetic for female patients undergoing outpatient laparoscopy under general anesthesia. We further conclude that 20 μg/kg is the optimum dose of droperidol for this purpose. Neither droperidol in the doses we have used, up to 20 μg/kg, nor metoclopramide (5 or 10 mg) significantly increased discharge time, compared to the group that received only placebo. We also conclude that metoclopramide (5 or 10 mg) has no effect on the incidence of nausea and vomiting given alone or in combination with droperidol.

References

1. Metter SE, Kitz DS, Young ML, Baldeck AM, Apfelbaum JL, Leeky JH. Nausea and vomiting after outpatient laparoscopy: incidence, impact on recovery stay and cost. Anesth Analg 1987;66:S116.

2. Doze VA, Shafer A, White PF. Nausea and vomiting after outpatient anesthesia: effectiveness of droperidol alone and in combination with metoclopramide. Anesth Analg 1987;66:S41.

3. Pandit SK, Kothary SP, Pandit UA, Mathai MK. Comparison of fentanyl and butorphanol for outpatient anaesthesia. Can J Anaesth 1987;34:130-4.

4. Abramowitz MD, Oh TH, Epstein BS, Rutterman UE, Friendly DS. The antiemetic effect of droperidol following outpatient strabismus surgery in children. Anesthesiology 1983;59:579-83.

5. Cohen SE, Woods WA, Wyner J. Antiemetic efficacy of droperidol and metoclopramide. Anesthesiology 1984;60:67-9.

6. Lucida R, Goodarzi M, Seleny F. Effect of low dose droperidol on postoperative vomiting in children. Can Anaesth Soc J 1981;28:259-62.

7. Korttila K, Kauste A, Auvinen J. Comparison of domperidone, droperidol and metoclopramide in prevention and treatment of nausea and vomiting after balanced anesthesia. Anesth Analg 1979;58:396-400.

8. Mortensen PT. Droperidol (dehydrobenzperidol®): postoperative antiemetic effect when given intravenously to gynecologic patients. Acta Anaesthesiol Scand 1982;26:48-52.

9. Korttila K, Linnoila M. Skills related to driving after intravenous diazepam, flunitrazepam or droperidol. Br J Anaesth 1974;46:961-9.

10. Assaff RAE, Clarke RSJ, Dundee JW, Samuel IO. Studies of drugs given before anaesthesia XXIV: metoclopramide with morphine and pethidine. Br J Anaesth 1974;46:514-9.

11. Madej TH, Simpson KH. Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following gynecological surgery in day cases. Br J Anaesth 1986;58:879-83.

12. Clark MM, Storrs JA. The prevention of postoperative vomiting after abortion: metoclopramide. Br J Anaesth 1964;41:890-3.

13. Ellis FR, Spence AA. Clinical trials of metoclopramide (Maxolon) as an antiemetic in anaesthesia. Anaesthesia 1970;25:368-71.

14. Pandit SK, Kothary SP, Pandit UA, Mirakhur RK. Premedication with cimetidine and metoclopramide. Anaesthesia 1986;41:486-92.

15. Rao TLK, Suseela M, El-Etr AA. Metoclopramide and cimetidine to reduce gastric juice pH volume. Anesth Analg 1984;63:S264.

16. Wetchler BV. Problem solving in postanesthesia care unit In: Wetchler BV, ed. Anesthesia for Ambulatory Surgery. Philadelphia: J.B. Lippincott, 1985:275-320.

17. Winning TJ, Brock-Utne JG, Downing JW. Nausea and vomiting after anesthesia and minor surgery. Anesth Analg 1977;56:674-7.

18. Lerman J, Eustis S, Smith DR. Effect of droperidol pretreatment on postanesthetic vomiting in children undergoing strabismus surgery. Anesthesiology 1986;65:322-5.

19. Dupre LJ, Stieglitz P. Extrapyramidal syndromes after premedication with droperidol in children. Br J Anaesth 1980;52:831-3.

20. Siker ES, Wolfson B, Stewart WD, Ciccarelli HE. The effects of fentanyl and droperidol alone and in combination on pain thresholds on human volunteers. Anesthesiology 1968;29:838.

21. Morrison JD, Clarke RSJ, Dundee JW. Studies of drugs given before anaesthesia. XXI droperidol. Br J Anaesth 1970;42:730-5.

22. Albibi R, McCullum RW. Metoclopramide: pharmacology and clinical application. Ann Int. Med. 1983;98:86-95.

An Unusual Foreign Body in the Left Main Bronchus after Open Heart Surgery

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An iatrogenic foreign body in the airway during the course of an anesthetic or in the postoperative period is a rare complication. We report a case of an unusual foreign body in the airway following coronary artery bypass grafting surgery.

Report of a Case

A 38-year-old male patient underwent emergency coronary artery bypass grafting surgery. He was 185 cm tall and weighed 98 kg. The patient was intubated with an 8.5 mm I.D. Mallinckrodt (Critical Care, Glen Falls, NY) disposable cuffed endotracheal tube, and the anesthetic course was uneventful. After surgery was completed, a chest radiograph taken in the operating room was essentially normal; no foreign bodies were seen. The patient was transferred to the surgical intensive care unit. During the transport, his ventilation was controlled with a self inflating bag (Laerdal resuscitation, Laerdal Medical Corporation, Armonk, NY).

In the intensive care unit, the patient was connected to a Bear I ventilator (Bear Medical Systems, Inc., Riverside CA), utilizing an intermittent mandatory ventilation mode. The ventilator was set at a tidal volume of 1000 ml with a respiratory rate of 10, an FIO_2 of 0.5 and a positive end expiratory pressure of 5 cm H_2O. Humidification was provided by a Puritan-Bennett Cascade humidifier (Bennett Respiration Products, Inc., Santa Monica, CA). Next morning,

the initial humidifier was replaced by a second Cascade humidifier. (The reason for this replacement could not be ascertained.)

A posterior-anterior view chest radiograph taken on the early morning of the first postoperative day showed a radio-opaque foreign body in the left chest; at that time it was not clear whether the foreign body was inside or outside of the patient. Because the patient had no signs or symptoms of airway obstruction or respiratory distress, it was assumed that the foreign body was outside of the patient. Two hours later, the patient was awake, his ventilatory functions and blood gas tensions were adequate, and his endotracheal tube was connected to a T-piece with a CPAP of +5 cm H_2O. An hour later the patient was extubated, and heated aerosol with an FIO_2 of 0.6 was provided. The patient was in the supine position from the time he arrived in the intensive care unit to the time he was extubated.

Another posterior-anterior view chest radiograph taken that afternoon showed ill defined small infiltrates in the lower lobes and a foreign body in the shape of a small coiled spring (Fig. 1). Additional PA and lateral views of the chest confirmed the location of the foreign body in the left lower lobe bronchus.

The patient was brought back to the operating room, given general anesthesia, and intubated with an 8.5 mm I.D. cuffed endotracheal tube. Fiberoptic bronchoscopy revealed the spring coil to be attached to the left mainstem bronchial mucosa. Removal was accomplished through a rigid bronchoscope by inflating a Fogarty catheter distal to the coil and withdrawing the catheter and the coil together. The rest of the postoperative course of the patient was normal, and the patient was discharged home on the 8th postoperative day.

The foreign body was found to be a metal spring with four helical turns. It was 8 mm in diameter and 10 mm in length (Fig. 2). Immediately, efforts were made to identify the source of this foreign body.

Figure 1. Posterior-anterior chest radiograph taken on the morning of postoperative day 1. Arrow points to foreign body in the left lower lobe bronchus.
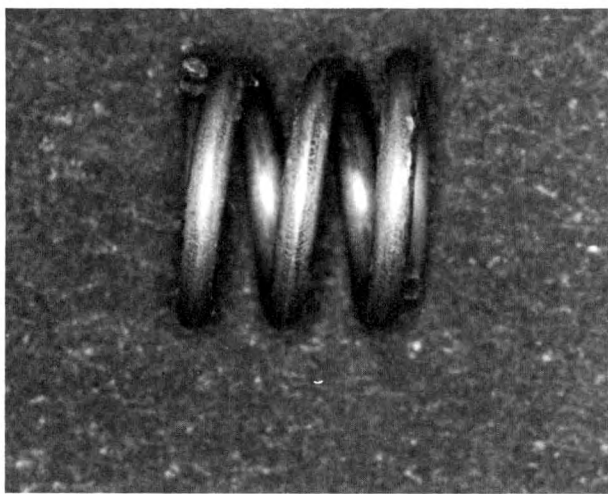
Figure 2. Foreign body after its removal by bronchoscopy.

Figure 3. **Top,** Exploded drawing of the lid clip assembly. **Bottom,** Lid clip assembly from cascade humidifier.

Springs from common items such as ball point pens, pagers, pilot balloons of endotracheal tube cuffs, laryngoscope handles, and the Wright respirometer were found to be either too small or too large. The self-inflating bag used during transport of the patient from the operating room did not have a spring coil. The Bear I ventilator used on the patient was completely dismantled and various parts were thoroughly examined.

The Cascade humidifier has two compression springs on either side to hold the lid clip assembly snug to the heater housing (Fig. 3A and B). Each spring is secured medially by a plastic shaft and laterally in a well on the external lid surface (Fig. 4A and B). Each one of these springs is 10 mm long, 8 mm in diameter, has the same number of helical turns, and weighs the same as the spring removed from the patient. Attempts to pass the spring through various sizes of endotracheal tubes revealed that it could go through an 8.5 mm I.D. tube longitudinally but not horizontally and it could not go through an 8 mm I.D. tube. The second Cascade humidifier used on the patient was found to have intact springs and the attempts to locate the first Cascade humidifier failed.

This case report describes the presence of a spring coil in the patient's tracheobronchial tree during mechanical ventilation in the immediate postoperative period. Efforts to identify the source of the spring coil revealed that it came from the Cascade humidi-

likely because the humidifier is mounted below the level of the supine patient and it is common practice at our institution to disconnect and drain water through the distal ends of the tubing. A more likely possibility is that one of the two sharp ends of the spring that fell outside the humidifier might have gotten attached to the clothing of one of the personnel taking care of the patient and entered the endotracheal tube longitudinally when the tube was disconnected either for suctioning or during measurements of respiratory parameters.

Iatrogenic foreign bodies entering the tracheobronchial tree are uncommon, but have been reported previously. Pieces of rubber after rupture of endotracheal tube cuffs (1,2), various parts of spray nozzles (3–5), distal portions of an armored endotracheal tube, (6) and a Laryng-O-Jet spray (7) entering the airway during anesthesia have been reported. Aspiration of a nasal airway by a patient in the intensive care unit has also been reported (8).

The report of this complication once again emphasizes the importance of carefully examining and testing all equipment for loose connections or broken components prior to use in patients. Tracheal intubation provides an unobstructed access for foreign bodies to enter the tracheobronchial tree. Anesthesiologists and other personnel involved in the care of intubated patients in the operating room or in intensive care units should be cognizant of such a possibility at all times.

Figure 4. **Top,** Cut-away drawing of the lid clip assembly. **Bottom,** Position of the spring in the lid clip assembly.

fier. How this spring coil got into the left bronchus is puzzling. The remote possibility of someone deliberately placing the spring in the endotracheal tube cannot be excluded. We hypothesize that the first humidifier had malfunctioned and was replaced because of a broken plastic shaft which released the spring coil. When the spring coil comes off the plastic shaft, it should fall outside the humidifier; if for some reason it falls inside the humidifier, it is most likely to go to the bottom of the canister, rather than be carried into the tubing and past the high point at the support arm and into the endotracheal tube. The spring could have fallen onto the top of the new housing and entered the corrugated tubing during the installation of the new humidifier. When excess water from condensed humidity was drained, the spring could have entered the patient's airway. This is very un-

References

1. Smotrilla MM, Nagel EL, Moya F. Failure of inflatable cuff resulting in foreign body in the trachea. Anesthesiology 1966;27: 512–3.

2. Doyle LA, Conway CF. A hazard of cuffed endotracheal tubes. Anaesthesia 1967;22:140–1.

3. Francis JG. A wandering spray nozzle. Br J Anaesth 1967;39: 813–4.

4. Paymaster NJ. A serious potential hazard of the MacIntosh laryngeal spray. Br J Anaesth 1972;44:1333.

5. Liew PC. A hazard due to commercially available topical spray. Anaesthesia 1973;28:346.

6. Yeung ML, Lett Z. An uncommon hazard of armored endotracheal tubes. Anaesthesia 1974;29:186–7.

7. Hard C, Nargozian CD. Iatrogenic airway foreign body. Anesthesiology 1984;61:786–7.

8. Hayes JD, Lockrem JD. Aspiration of nasal airway: a case report and principles of management. Anesthesiology 1985;62:534–5.

Jaundice, Oximetry, and Spurious Hemoglobin Desaturation

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Spectrophotometric differential analysis of hemoglobin (as measured by co-oximeter) gives the percentages of oxyhemoglobin, methemoglobin (MetHb), and carboxyhemoglobin (COHb) and is used as a standard for comparing other methods of measurement of oxyhemoglobin. We observed that spectrophotometry gives spuriously low oxyhemoglobin and high methemoglobin values in the presence of hyperbilirubinemia.

Oximetry provides accurate assessment of oxygen saturation and allows moment to moment monitoring of oxygen therapy. Several studies have demonstrated excellent correlation between pulse oximetry and spectrophotometric differential analysis (co-oximetry) (Co-oximeter® 282, Lexington, MA) (1-3).

However, with any measurement technique there are limitations, and pulse oximetry is no exception. Such limitations have been extensively investigated and may be grouped into the dyshemoglobinemias, inadequate pulse detection, extraneous light sources, patient movement, and intravenous dye administration (4-6). In general, co-oximetry is believed to provide a more accurate result in these situations, except in the case of intravenous dye administration where neither technique is accurate. We present the following cases to demonstrate that in the presence of severe hyperbilirubinemia, pulse oximetry may be more accurate than co-oximetry.

Case Report 1

The patient was a 24-year-old white man suffering from nodular sclerosing Hodgkin's lymphoma. His course was marked by several rounds of chemother-

apy and eventual whole body irradiation with autologous bone marrow transplantation. Subsequent development of hepatic venous occlusive disease had culminated in hepatic failure (bilirubin 37-42 mg%) and respiratory failure necessitating intubation of the trachea and mechanical ventilatory support. Monitoring included continuous pulse oximetry with intermittent blood gas analysis, and co-oximetry determined oxygen saturation.

Despite PaO_2s ranging from 92-133 mm Hg, co-oximetry derived saturations (88-93%) bore no consistent relationship to PaO_2. Pulse oximetry demonstrated 98-99% saturations on devices from two manufacturers (Nellcor N100c and Ohmeda Biox 3700). More complete co-oximetry demonstrated slight elevations of carboxyhemoglobin (2.4-2.9%), but more pronounced elevations of methemoglobin (MetHb) (3.2-11.9%) (Table 1). History and drug exposure were inconsistent with the development of MetHb, and addition of the reducing agent sodium dithionite, which normally reduces methemoglobin to hemoglobin, had no effect on the measured MetHg levels. Subsequently, icteric serum separated from a fresh sample and passed through the co-oximeter was read as MetHb 105% and CoHb 17.6%. Control serum measured MetHb 0% and COHb 5%. It was believed that the elevated bilirubin levels were interfering with co-oximetry, leading to artifactual increases of MetHb.

Case Report 2

The patient was a 16-year-old anephric white woman maintained on chronic dialysis who had suffered a bout of intestinal obstruction and intraabdominal sepsis. After jejunostomy and tense abdominal closure, the patient required prolonged mechanical support of ventilation. Hepatic failure (bilirubin rose to 44 mg%) developed and again, despite PaO_2 of 90-117 mm Hg and pulse oximetry saturations of 97-99%, co-oximetry demonstrated saturations of 92-93% with MetHb 3-4% and COHb 2-3.5% (Table 1). There again was no inciting cause found, and artifactual elevation of MetHb and COHb by the interfering bilirubin was again believed to be the cause.

Table 1. Analysis of Arterial Blood Gases, Hemoglobin Saturation on Co-oximetry, Hemoglobin Saturation by Pulse Oximetry, and Serum Total Bilirubin

Day	PaO$_2$ (mm Hg)	PaCO$_2$ (mm Hg)	pH	BE	SaO$_2$ (%)	MetHb (%)	COHB (%)	SpO$_2$ (%)	Bili Total (mg dl)
Patient 1 Samples									
1 a	92	49	7.34	+1	93	3.2	2.7	99	41
b	103	50	7.33	0	92	6.5	1.0	99	
c	99	53	7.33	+2	92	4.0	2.4˙	98	38
2	104	51	7.35	+2	88	11.1	1.1	98	45
3	123	48	7.38	+2	94	3.3	2.5	99	42.8
4	128	46	7.40	+3	89	11.9	2.9	99	37.8
Patient's serum					3.6	105	17.6		37.8
Control serum					0	0	5.0		
Patient 2 Samples									
1	82	32	7.37	−4	92.9	3.3	3.5	97	44.4
2	107	35	7.41	−4	92.3	3.4	2.2	97	36
3	117	32	7.37	−4	92.8	3.9	2.9	98	39

COHb = Percentage of carboxyhemoglobin measured by co-oximeter; MetHb = Percentage of methemoglobin measured by co-oximeter; SaO$_2$ = Percentage hemoglobin saturation with oxygen measured by co-oximeter; SPO$_2$ = Percentage of hemoglobin saturation with oxygen measured by pulse oximetry.

Discussion

From these results, it would appear that severe hyperbilirubinemia may indeed interfere with co-oximetry and be interpreted as falsely elevated MetHb and perhaps COHb levels. There appeared to be no such effect on pulse oximetry. Knowledge of the principles and limitations of pulse oximetry and co-oximetry may help explain this phenomenon.

The IL 282 Co-oximeter (Instrumentation Laboratory) utilizes a four wavelength system, measuring *absolute* absorbance at each of four distinct wavelengths (535, 585, 594, and 626 nm). Through application of Beer's law, four linear equations of absorption are solved simultaneously for four independent variables (7). Thus, up to four hemoglobin species may be determined. An extraneous interfering substance could alter this determination based on how much its absorption spectrum overlapped the measured wavelengths. In so doing, it could be mistaken for one of the hemoglobin variants because the system assumes that only four variants are present. An examination of bilirubin's absorption curve demonstrates a strong peak at 450 nm, which is outside the measured range, but a tail that extends into the 535–585 nm range may account for our observed interference.

Pulse oximetry, on the other hand, measures *relative* absorbance at only two wavelengths (660 and 940 nm) and precisely derives a ratio of the absorbancies at these two wavelengths. Through a calibration curve it relates this ratio to degree of oxygen saturation. It is thus able to delineate only two hemoglobin variants: reduced hemoglobin and oxyhemoglobin. If an interfering substance did not significantly alter this ratio, either by contributing minimally to absorbance at 660 and 940 nm or contributing equally, then it would be expected to have little effect on measured saturations. Bilirubin has minimal absorption at 660 and 940 nm, and therefore has no effect on the derived ratio. It is probably for this reason that bilirubin has little effect on pulse oximetry. We present these cases to alert clinicians to the fact that co-oximetry may not be reliable in the presence of severe hyperbilirubinemia.

References

1. Yelderman M, New W jr. Evaluation of pulse oximetry. Anesthesiology 1983;59:349-52.
2. Brodsky JB, Shulman MS, Swan M, Mark JPD. Pulse oximetry during one lung ventilation. Anesthesiology 1985;63:212-4.
3. Mihm FG, Halperin BD. Noninvasive detection of profound arterial desaturations using a pulse oximetry device. Anesthesiology 1985;62:83-7.
4. Barker SJ, Tremper KK, Hufstedler S, et al. The effects of carbon monoxide inhalation on noninvasive oxygen monitoring. Anesth Analg 1986;65:512.
5. Scheller MS, Unger RJ, Kelner MJ. Effects of intravenously administered dyes on pulse oximetry readings. Anesthesiology 1986;65:550-2.
6. Brooks TD, Paulus DA, Winkle WE. Infrared heat lamps interfere with pulse oximeters. Anesthesiology 1984;61:630.
7. Pologe JA. Pulse oximetry: technical aspects of machine design. Int Anesthesiol Clin 1987;25:137-53.

Effect of Diluent Volume on Analgesia Produced by Epidural Fentanyl

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Injection of opioids into the epidural space produces postoperative analgesia by acting on receptors in lamina II, IV, and V of the substantia gelatinosa (1). Morphine, due to its low lipid solubility produces numerous side effects when injected into the epidural space; most notably delayed respiratory depression (2). Fentanyl, a highly lipid soluble narcotic agonist, has a more rapid onset of action and a significantly lower incidence of side effects than those of morphine. In a dose-response study in patients after cesarean delivery, 50 μg of epidural fentanyl was found to provide maximal analgesia with minimal incidence of side effects (3). The effect of varying the volume of injectate on the onset, duration, and incidence of side effects produced by 50 μg of fentanyl has not been reported. This standard dose of fentanyl diluted in larger volumes could increase the surface area of drug exposure and thus augment the number of opioid receptors affected. Conversely, diluting the opioid in greater volume may reduce the concentration gradient between the central nervous system and epidural space and thereby decrease both the rapidity of onset and duration of analgesia. Fentanyl is being given epidurally in several different dilutions. To determine the most effective diluent volume, a double-blind, randomized study was undertaken with varying volumes of normal saline solution to dilute a single 50 μg dose of epidural fentanyl.

Methods

The study was approved by the hospital committee for the protection of human subjects from research risks and written informed consent was obtained. Thirty ASA physical status I patients scheduled for elective cesarean (singleton) delivery under epidural anesthesia were enrolled in the study. Two patients were excluded from the study when the epidural failed to achieve adequate surgical anesthesia. The 28 remaining patients were randomly assigned to one of seven study groups (4 patients per group). Before induction of anesthesia, an intravenous catheter was inserted and each patient received a minimum of 1,500 ml of lactated Ringer's solution at room temperature. Anesthesia was induced via an epidural catheter inserted at the $L_{2,3}$ or $L_{3,4}$ interspace. Sensory anesthesia (determined by pinprick) to the fourth thoracic dermatome was achieved with incremental doses of 2% lidocaine with 1:200,000 epinephrine. The average local anesthetic volume was 25 ml. Blood pressure was maintained at the patient's pre-epidural baseline with incremental intravenous doses of ephedrine, as required.

Patients were evaluated with the use of a 10 cm visual analog pain scale (VAS) (4). After completion of surgery, when a patient reported a pain score of 3 or greater, either in the operating room or in the recovery room, they were given the study drug. If the patient was still comfortable at the completion of surgery, the epidural catheter was left in place, and the patient was given the study drug in the recovery room when her pain score reached 3. If the patient complained of pain intraoperatively, a second dose of local anesthetic was administered via the epidural catheter. If this second dose of lidocaine was necessary, the epidural catheter was once again left in place at the completion of surgery so that the study drug could be given in the recovery room when the patient had a pain score of 3. The study drug consisted of 50 μg of fentanyl diluted in preservative free

normal saline solution to a total volume of 1 (no dilution), 2, 5, 10, 15, 20, or 25 ml. The injection of this drug into the epidural space was immediately followed by injection of 0.5 ml of air to clear the catheter. Vital signs, level of sensory anesthesia as defined by pin prick, motor block (following Bromage's criteria) (5), and the patient's subjective pain score (VAS) were recorded. The presence of side effects including nausea, shivering pruritis, somnolence, and respiratory depression were also recorded. Respiratory depression was defined in this study as a respiratory rate of less than 10 breaths/minute or desaturation as detected by finger pulse oximetry. The anesthesiologist recording the data was blinded to the diluent volume that had been injected. The time to onset of analgesia was defined as the time it took after injection of the study drug until the patient became comfortable (a pain score of 0). The duration of analgesia, defined as the time from the onset of analgesia to the time when the patient requested supplemental pain medication (VAS of 3) was also noted. When the patient stated that her pain had returned, she was given a parenteral opioid according to the routine postoperative obstetric orders. The amount of parenteral opioid administered over 24 hours was recorded in an effort to determine whether any long acting effect of the epidural narcotic existed. To allow for comparison, all opioid drugs were converted to "morphine equivalents" using the following scale: 100 mg meperidine = 10 mg morphine = 1.5 mg hydromorphone. The data were analyzed for statistical significance using an analysis of variance, and regression curves were calculated for best fit to the data ($P < 0.05$ was considered significant).

Results

The patients in each study group were similar demographically with respect to weight, height, age, parity, and preoperative temperature. Figure 1 shows the time to onset of analgesia for varying volumes of injectate where a superimposed logarithmic regression line was calculated for best fit. Total volumes of less than 5 ml were associated with a significantly longer time to onset of analgesia.

Two of the patients in the 1-ml group and one of the patients in the 2-ml group reported that their pain, although improved, did not return to a VAS score of 0 (e.g., VAS score of 1 or 2) after the epidural fentanyl was given. (Subsequent, correct epidural catheter position was confirmed with a local anesthetic test dose.)

Figure 2 shows the duration of analgesia related to volume of injectate. Volumes < 5 ml were associated
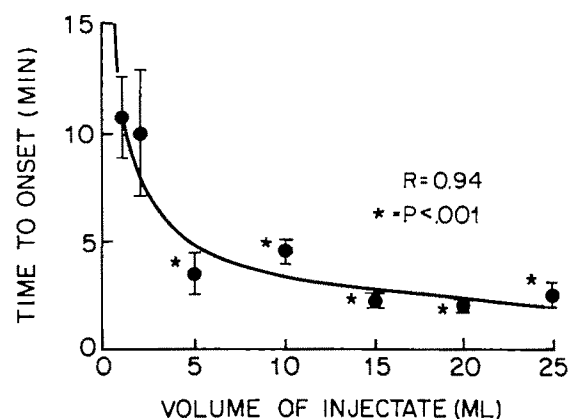
Figure 1. The time to onset of analgesia versus the total volume of injectate. A logarithmic regression line is superimposed. Each group was compared to the control group (1 ml fentanyl undiluted).
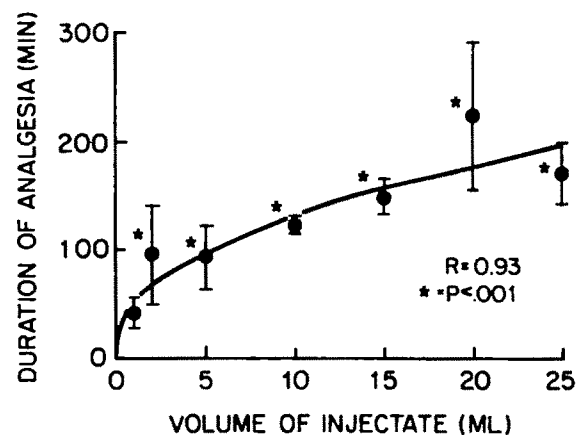
Figure 2. The duration of analgesia versus the total volume of injectate. A logarithmic regression line is superimposed. Each group was compared to the control group (1 ml fentanyl undiluted).

with significantly shorter durations of analgesia than volumes >10 ml. Volumes >20 ml were associated with the longest duration.

No significant reduction in the 24-hour opioid dose was seen irrespective of the diluent volume. The total dose of opioid over the first 24-hours postoperatively ranged from 20 to 50 mg of morphine equivalents. In this study, level of sensory block and duration of motor block were unaffected by varying diluent volume.

Neither somnolence nor respiratory depression was seen in any of the study patients. Three patients noted mild pruritus after epidural injection of 50 mcg of fentanyl (5-ml, 10-ml, and 20-ml group); no treatment was required. One patient experienced nausea about 10 minutes after the epidural study drug injection (15-ml group); this resolved within 5 minutes with no treatment required.

Discussion

Fentanyl is often given epidurally to manage postoperative pain after cesarean delivery. The optimum volume in which to dilute the standard dose of epidural fentanyl has not been previously determined. The purpose of this study was to assess the effect of varying the volume of diluent added to a standard dose of 50 μg of fentanyl on onset and duration of analgesia, 24-hour total opioid requirement, and incidence of side effects.

One could postulate that by increasing the volume of diluent, the time to onset of analgesia would be increased and the duration of analgesia would be reduced due to a decrease in the concentration gradient for diffusion from epidural to subarachnoid space (6). The opposite was observed. Increasing the volume of diluent (and thus injection of a less concentrated fentanyl solution) produced a significantly more rapid onset and longer duration of analgesia. The explanation for these findings may be related to the high lipid solubility of fentanyl. Increasing the volume in which a standard dose of fentanyl is diluted may physically shorten the time to onset of analgesia by augmenting the rate of diffusion of fentanyl into the central nervous system. Larger diluent volumes may increase the initial spread of the solution in the epidural space resulting in a larger number of opioid receptors affected.

The majority of study patients required supplemental pain relief within 3 hours regardless of diluent volume. No significant difference in the 24-hour opioid requirement was seen between the different study groups. This confirms that a single dose of epidural fentanyl is not a long acting analgesic, and no amount of diluent will produce this. However, by increasing the diluent, one can speed the onset of patient comfort, and by achieving 3 hours of postoperative analgesia, one can obviate the necessity for repeated parenteral opiate injections in the recovery room.

In summary, epidural fentanyl has been given in various volumes and dilutions for postoperative analgesia. In this study, use of diluent volumes less than 5 ml was associated with significantly longer time to onset of analgesia and significantly shorter duration of analgesia. No respiratory depression was seen in any of the study patients and the incidence of side effects (nausea and pruritis) appeared independent of diluent volume. This study supports the practice of dilution of a standard epidural dose of 50 μg of fentanyl in at least 10 ml of preservative free saline solution to shorten the time to onset and maximize the duration of analgesia.

References

1. Game CJA, Lodge D. The pharmacology of the inhibition of dorsal horn neurones by impulses in mylinated cutaneous afferents in the cat. Exp Brain Res 1975;23:75–84.

2. Gustafsson LL, Schildt B, Jacobsen KJ. Adverse effects of extradural and intrathecal opiates. Br J Anaesth 1982;54:479–86.

3. Naulty JS, Datta S, Ostheimer GW, Johnson MD, Burger GA. Epidural fentanyl for post cesarean delivery pain management. Anesthesiology 1985;63:694–8.

4. Revill SJ, Robinson JO, Rosen M. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31:1191–8.

5. Bromage PR, Burfoot MF, Crowell DE. Quality of epidural blockade: I. Influence of physical findings. Br J Anaesth 1984;36:342–52.

6. Moore RA, Bullingham RSJ, Hand CW, et al. Dural permeability to narcotics: in vitro detection and application to extradural administration. Br J Anaesth 1982;54:1117–28.

Osteogenesis Imperfecta and Hyperthermia

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Children with osteogenesis imperfecta (OI) are at high risk during anesthesia for a number of physiological and anatomical reasons. In addition to their propensity for developing fractures, neck and jaw mobility may be restricted by deformity (1). Severe thoracic distortion and kyphoscoliosis may restrict pulmonary function although ventilation-perfusion is usually normal (2). Other associated anomalies such as dentinogenesis imperfecta, cleft palate, premature atherosclerosis (3), and valvular heart disease (4,5) may increase the hazards of anesthesia.

Anesthesia-induced hyperthermia has also been observed in patients with OI (6). In 1973 Solomons and Myers reported a four-year-old girl with OI who developed fever (maximum 39.5°C) and tachycardia (maximum 144 bpm) on two occasions during anesthesia (6). Premedication consisted of pentobarbitone and scopolamine, while induction and maintenance was with halothane and nitrous oxide. Serum creatinine phosphokinase (CPK) levels were not measured; muscle rigidity was not prominent and the temperature responded to active cooling. Based on this report, it has been stated that the hyperthermia during anesthesia in patients with OI does not progress to malignant hyperthermia (MH). However, a probable case of MH has been described in a young man with a mild form of OI (7).

We present a young girl with severe OI who had a hyperthermic reaction in the intensive care unit following anesthesia. Although she did not have classi-

cal MH, her clinical course followed a malignan pattern, requiring energetic resuscitation.

Case Report

This severely deformed 7 year-old girl with Type 3 O tarda (1) was transferred from a peripheral hospita where she was admitted following a fall from he sister's arms. In the emergency room she was aler and responsive (Glasgow coma scale = 12). She wa: afebrile (36.4°C), systolic blood pressure was 120 mn Hg, heart rate was 80 bmp, and respiratory rate wa: 30/min. She had a large hematoma over the lef parietal area with an underlying depressed skul fracture. Her left pupil was larger than the right anc reacted sluggishly to light. An emergency CT scan o the head showed a large left epidural hematoma witl compression of the cortex and she was immediatel) transferred to the operating room (OR) for evacatioi of the clot.

Her response to anesthesia and subsequent cours(is presented in the figure. Upon arrival in the OR he heart had increased to 130 bpm, mean arterial pres sure was 80 mm Hg, and temperature was 36.4°C After preoxygenation, anesthesia was induced witl thiopental and maintained with isoflurane and ni trous oxide. Atropine (0.01 mg/kg) and succinylcho line were administered and a nasotracheal tube in serted. Masseter spasm did not occur followin{ succinylcholine and muscle relaxation intra-opera tively was achieved with atracurium. The anestheti course was notable for a 30-bpm increase in heart rat(and a 1.6°C increase in temperature, such that by th(end of surgery, her heart rate had increased to 16(bpm and temperature to 38°C.

She was returned to the intensive care unit, intu bated and hyperventilated, but no longer paralyzed Over the next hour she developed a sinus tachycardi; of 212 bpm. She became hypotensive and pale, hy poxic (PaO_2 = 47 mm Hg) and developed a metaboli acidosis (base excess = −12 mEq/l). $PaCO_2$ remainec between 23–28 mm Hg and a femoral venous PCO
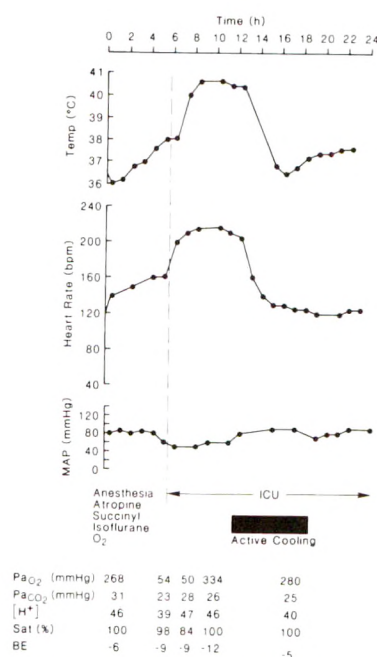
Figure 1. Clinical course of the patient during anesthesia and in the intensive care unit (ICU). Hemodynamic stability was not restored until her temperature responded to active cooling measures. MAP, mean arterial pressure.

was 42 mm Hg. There was no evidence of muscle rigidity, although this was difficult to exclude because of poor muscle mass. Packed red blood cells (15 ml/kg) and 5% albumin (10 ml/kg) were administered on the suspicion of intra-abdominal bleeding. Mean arterial blood pressure increased to 60 mm Hg from 50 mm Hg and hemoglobin increased to 140 gm/l from 100 gm/l following the blood transfusion. However, the tachycardia did not decrease in response to volume administration and her heart rate remained >200 bpm. A 12-lead electrocardiogram showed a sinus tachycardia with a normal axis and no evidence of myocardial infarction.

At this stage active measures were undertaken to reduce her temperature which had increased to 40.6°C (see Fig. 1). She was paralyzed with vecuronium, and cooled with a cooling blanket, topical ice packs, and ice-cold gastric lavages. Sodium bicarbonate (2 mEq/kg) was administered to correct the metabolic acidosis and she was reintubated with a larger endotracheal tube, following which her oxygenation improved. A subsequent whole body CT scan showed no evidence of internal hemorrhage.

Within 2 hours of commencing active cooling measures, rectal temperature decreased to 36°C, heart rate decreased to 120/min, and the metabolic acidosis had resolved. She was extubated 24 hours later and remained well with occasional spikes in temperature

up to 38°C but without any adverse effects. Blood cultures were negative.

Serum creatinine phosphokinase (CPK) was 2232 IU/l during the hyperthermic episode. Less than 4% consisted of CK-MB fraction. Serum aspartate transaminase (AST) level (>2750 U/l) was also above normal limits but with normal liver function tests. Within 24 hrs serum levels of these enzymes had decreased to 293 IU/l and 580 IU/l, respectively, and were within normal limits within a week. This enzymatic pattern is consistent with skeletal muscle involvement. Myoglobin was present in the urine but only on the day of crisis. Thyroid function studies were normal.

There was no family history of malignant hyperthermia. Her mother had been told that the patient's heart rate had increased during previous anesthetics for various orthopedic and dental procedures. A review of 7 previous anesthetics showed that the girl's heart rate was never higher than 170 bpm and her temperature never went above 38°C. Anesthesia on these occasions included administration of thiopental, succinylcholine, atropine, fentanyl, morphine, oxygen and nitrous oxide, and halothane. Serum CPK levels of the patient's mother, father, and sister were normal. Muscle biopsies were not obtained.

Discussion

MH is a familial disease occurring in people who have a generalized membrane abnormality. Patients with certain myopathies are at risk (8,9) and the condition is more common among children (10). MH is not a uniform entity. Instead, it represents a spectrum of disorders ranging from the "classic" case to those with unusual presentations and mild symptomatology. Less than 10% of all cases of MH progress to the fulminant variety (11). The basic underlying pathophysiology is similar in both fulminant and mild cases of MH and is related to increased intracellular calcium ion concentration although the cause of the release of calcium into the cell is not understood (12).

A hypermetabolic state, unrelated to anesthesia, and represented clinically by excessive diaphoresis, mild hyperthermia, tachycardia, and tachypnea, has been documented in children with OI (13). Increased oxygen consumption, elevated serum thyroxin levels and evidence of a disturbance of high-energy phosphate metabolism have been observed. The cause of this hypermetabolic state is unknown.

It is possible that patients with OI may have an underlying metabolic abnormality which predisposes

them to sustained muscle contraction following the stimulus of a variety of drugs, similar to other individuals identified as being MH susceptible (MHS). It is of interest that patients with OI share certain characteristics with individuals who have developed MH. These similarities include autosomal dominant or recessive inheritance, connective tissue abnormalities, and elevated levels of serum inorganic pyrophosphate (14). MH has been reported in isolated individuals with OI (7), while Rosenberg found one of 5 patients with OI, in whom muscle biopsies were performed, to be MH susceptible (12).

Although the girl reported here did not have classical MH, her clinical course was similar to MH with fever, tachycardia, hypoxia, acidosis, and elevated levels of serum CPK. However, she did not develop masseter rigidity with succinylcholine and muscle rigidity was not present. In addition, respiratory acidosis, one of the hallmarks of MH, did not occur. There was no family history of MH and the family members had normal CPK levels. It is unlikely that her deterioration postoperatively was due to hypovolemia since she was not bleeding internally and her tachycardia was resistant to volume resuscitation but responded dramatically to cooling.

Because of the experience of Solomon and Myers, we did not administer dantrolene to this girl. However, in view of the established safety·of the drug, its use in these circumstances could not be criticized. Indeed, dePinna, elected to treat a 5-year-old boy with OI who had previous pyrexial responses to anesthesia, as a MHS individual. Triggering agents were avoided and prophylactic dantrolene was administered both preoperatively and postoperatively (15). Only mild temperature elevations occurred and serum CPK levels remained normal. Libman, in a review of the anesthetic management of patients with OI, supported this approach (16). An additional reason for caution and close monitoring of the acid-base status in these children is the occurrence of metabolic acidosis with anesthesia in children with OI, in the absence of hypoxia, hypercarbia, hypotension, or fever (17).

Because of the rarity of OI tarda [approximately 1: 25,000 live births (18)], it is difficult to determine its exact relationship to MH, an equally rare entity [1: 12,000 anesthesias in children (15)]. In an earlier review OI was listed as an MH associated condition (19); however, this report and others (7) appear to suggest that hyperpyrexia may occur in these patients during and after anesthesia, but does not progress to MH. In addition, although the hyperthermia of OI may be associated with major acid-base and cardiorespiratory disturbances, rapid stabilization

can be achieved by general supportive measures and whole body cooling.

The routine use of prophylactic dantrolene is probably not justified in these patients; however, certain drugs should be avoided. Apart from concerns about its possible role in the pathogenesis of hyperthermia succinylcholine may cause fractures in patients with OI as a result of muscle fasciculation. Pancuronium bromide or atracurium remain the muscle relaxants o choice (20). The use of anticholinergics should also be avoided because ·of the possible exacerbation of hy perthermia (13).

References

1. Loeber NV. Sofield osteotomy and osteogenesis imperfecta. In Slehling LB, ed. Common problems in pediatric anesthesia Chicago: Year Book Med Pub Inc., 1982:206-10.

2. Falvo FA, Klain DB, Krauss AN, Root L, Auld P. Pulmonary function studies in osteogenesis imperfecta. Am Rev Resp Di: 1973;108:1258-60.

3. McKusick VA. Heritable disorders of connective tissue. 3rd ed St. Louis: C.V. Mosby Co., 1966:230-70.

4. Heppner RL, Babitt HI, Bianchine JW, Warbasse JR. Aorti· regurgitation and aneurysm of sinus of Valsava associatec with osteogenesis imperfecta. Am J Cardiol 1973;31:654-6.

5. Wood SJ. Thomas J, Baimbridge MV. Mitral valve disease and open heart surgery in osteogenesis imperfecta tarda. Br Hear J 1973;35:103-6.

6. Solomons CC, Myers DN. Hyperthermia of osteogenesis im perfecta and its relationship to malignant hyperthermia. In Gordon RA, Britt BA, Kalow W, eds. Proceedings of the international Symposium on Malignant Hyperthermia. Spring field, Ill: CC Thomas, 1971:319-30.

7. Rampton AJ, Kelly DA, Shanahan EC, Ingram GS. Occurrence of malignant hyperthermia in a patient with osteogenesi: imperfecta. Br J Anaesth 1984;56:1443-4.

8. Frank JP, Harati Y, Butler IJ, Nelson TE, Scott CI. Central core disease and malignant hyperthermia syndrome. Ann Neuro 1980;7:11-7.

9. Kefler HM, Singer WD, Reynolds RN. Malignant hyperther mia in a child with Duchenne's muscular dystrophy. Pediatric: 1983;71:118-9.

10. Sessler DI. Malignant hyperthermia. J Pediatr 1986;109:9-14.

11. Ording H. Incidence of malignant hyperthermia in Denmark Anesthesia and Analgesia 1985;64:700-4.

12. Rosenberg H. Clinical presentation of malignant hyperther mia. Br J Anaesth 1988;60:268-73.

13. Cropp GJA, Myers DN. Physiological evidence of hypermetab olism in osteogenesis imperfecta. Pediatrics 1972;49:375-91.

14. Tan S, Aldrete JA, Solomons CC. Correlation of creatinine phosphokinase and pyrophosphate during surgery in patient: with malignant hyperthermia susceptibility. In: Aldrete JA, Britt BA, eds. Proceedings of the second international sympo sium on malignant hyperthermia, Denver, 1977. New York: Grune and Stratton, 1978:389-400.

15. dePinna GA. A case of osteogenesis imperfecta, malignant hyperthermia susceptible—anesthetic management. In: Aldrete JA, Britt BA, eds. Proceedings of the second international symposium on malignant hyperthermia, Denver, 1977. New York: Grune and Stratton, 1978:389-400.

16. Libman RH. Anesthetic considerations for the patient with osteogenesis imperfecta. Clin Ortho 1981;159:123-5.

17. Sadat-Ali M, Sankaran-Kutty M, Adu-Gyamfi Y. Metabolic acidosis in osteogenesis imperfecta. Eur J Pediatr 1986;145:324-5.

18. Smith DW. Recognizable patterns of human malformation: genetic, embryological and clinical aspects. 2nd edition. Philadelphia: W.B. Saunders and Co., 1976:286.

19. Rosenberg H. In: American Society of Anesthesiologists Refresher Course Lectures, 1985. American Society of Anesthesiologists Inc, 1985.

20. Michel PA, Fronefield HP. Use of atracurium in a patient susceptible to malignant hyperthermia. Anesthesiology 1985; 62:213.

Fifty-Eight Years Ago in

Anesthesia & Analgesia

Y. Henderson: The contribution of anesthetists to inhalation therapy; Current Researches in Anesthesia and Analgesia; 1931;10:56–8.

This is the text of a talk that Yandell Henderson, Professor of Applied Physiology at Yale University, presented to a meeting of the New York Society of Anesthetists (NYSA) in October 1930. The article states that the occasion was the 25th anniversary of the founding of the NYSA. Actually, what was founded in 1905 was the Long Island Society of Anesthetists. In 1911 the Long Island Society, however, changed its name. It became the NYSA. It was particularly appropriate that Henderson was a speaker on this occasion in 1930, since he also spoke at the meeting in 1911 at which the Long Island Society became the NYSA. His topic in 1911 was the relationship between physical chemistry and clinical anesthesia. In 1930 it was the role of anesthetists in inhalation therapy. In 1936 the NYSA in turn became the American Society of Anesthetists, which in turn became the American Society of Anesthesiologists in 1945.

Yandell Henderson was a widely known and respected American pioneer in respiratory physiology. His reputation was such that he was able to introduce a new and radical concept, namely, that direct communication between clinicians and basic scientists was necessary if fundamental physiologic discoveries were to be applied to and used in clinical practice in less than one generation. Today it is a given that the anesthesiologist is the physiologist and pharmacologist of the operating room, but this was not always so. Henderson had a special interest in anesthesia and anesthetists. With his clout and his preaching he was able to expand anesthetists' horizons from the mechanics of anesthetic techniques to physiologic principles. He did it in 1910, when, as chairman of one of the sections of the American Medical Association (AMA), he gave an address to the AMA entitled "Clinical Physiology—an Opportunity and a Duty." He did it in 1911 in his talk to anesthetists on physiological chemistry. He did it in an astonishingly insightful lecture on "Respiration in Anaesthesia: Control by Carbon Dioxide" (Br Med J 1925; 2:1170–5). He did it yet again in this, his 1930 talk, in which he emphasized the role of anesthetists in the management of respiration, the only bodily function, as he points out, susceptible (in 1930) to therapeutic control. In this 1930 talk, he urges anesthetists to function as physicians not just in the operating room but outside the operating room in prevention of postoperative respiratory depression and atelectasis, in treatment of carbon monoxide poisoning and in neonatal resuscitation. Heady stuff in 1930, an era when anesthetists were still wedded to the operating room, but an early harbinger of things to come.

Intraoperative Hypoxemic Spells in Tetralogy of Fallot

An Echocardiographic Analysis of Diagnosis and Treatment

William J. Greeley, MD, Thomas E. Stanley III, MD, Ross M. Ungerleider, MD, and Joseph A. Kisslo, MD

Systemic arterial oxygen saturation in patients with tetralogy of Fallot is influenced by changes in the dynamics of right ventricular outflow tract obstruction or changes in systemic vascular resistance (1). Intraoperative decreases in systemic vascular resistance due to hypotension or increases in right ventricular outflow tract obstruction due to increased sympathetic stimulation are associated with an increase in right-to-left shunting and a decrease in systemic arterial hemoglobin oxygen saturation (Sao_2), producing a hypoxemic or "tet" spell during anesthesia and surgery (2). The precise mechanisms of these spells and their treatment have been hypothesized but never demonstrated. We report two children with tetralogy of Fallot who had acute hypoxemic spells during anesthesia and surgery where dynamic changes in shunting and the effects of propranolol and phenylephrine therapy were observed for the first time by intraoperative two-dimensional echocardiography with color flow imaging (CFI).

Case 1

An 18-month-old male with tetralogy of Fallot (TOF) was anesthetized for complete repair of his defect. At the time of his operative procedure, the patient required no previous medical or surgical therapy for his cardiac lesion and had no other medical illnesses. Preoperative laboratory studies were normal. The

patient was premedicated with meperidine 2 mg/kg, pentobarbital 4 mg/kg, and diazepam 0.1 mg/kg orally 90 minutes before the induction of anesthesia. Anesthesia was induced with oxygen, nitrous oxide, and halothane by mask and maintained with fentanyl IV (75 μg/kg). Indwelling arterial and central venous catheters were placed for continuous pressure monitoring. Ventilation was controlled and neuromuscular blockade was maintained using incremental doses of pancuronium. Pulse rate (115–140 beats/min), blood pressure (90–120/60–75 mm Hg), systemic arterial oxygen saturation (91–97%) as measured by pulse oximetry, and central venous pressure (6–8 mm Hg) remained stable during skin incision and sternotomy. After placement of the arterial cannula of the extracorporeal circuit into the ascending aorta, blood pressure gradually decreased to 70/40 mm Hg over a 1–2 min interval. The decrease in blood pressure was accompanied by a decrease in central venous pressure and a marked reduction in Sao_2 to 75%. Epicardial echocardiography with CFI demonstrated a net right-to-left shunt through the ventricular septal defect (VSD) (Fig. 1). Diagnoses of hypovolemia and a secondary hypoxemic spell due to increased right-to-left shunting were made. Phenylephrine 25 μg, administered IV, resulted in an immediate increase in systemic arterial pressure (110/74 mm Hg) and an increase in Sao_2 to 100%, and an epicardial echocardiography with CFI that showed a reversal of shunting with a net left-to-right ventricular shunt (Fig. 2). The patient was subsequently given a bolus of lactated Ringer's solution and the remainder of the case proceeded uneventfully.

Case 2

A 3-year-old male with TOF was anesthetized for complete repair of his defect. At the time of his operative procedure, the patient required no prior
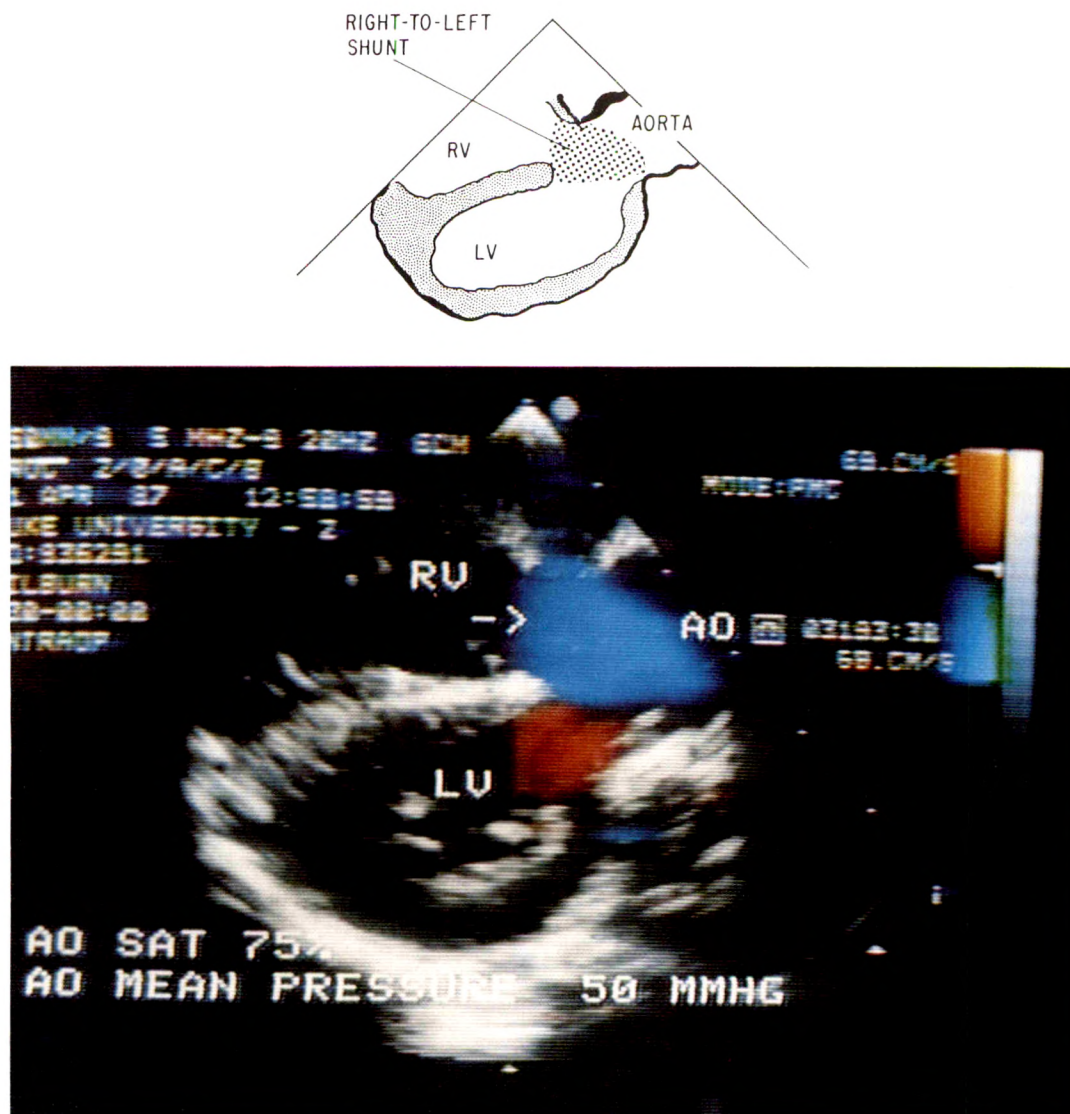
Figure 1. Doppler color flow map (left) and schematic diagram (right) of a modified long-axis view illustrating right-to-left shunting (blue jet) across the ventricular septal defect during systole. RV, right ventricle; LV, left ventricle.

medical therapy, had had no surgery for his congenital heart defect, and had no other medical illnesses. Preoperative laboratory studies were normal except for a hemoglobin of 16 g/dL and a hematocrit of 49%. Premedication consisted of meperidine 2 mg/kg, pentobarbital 4 mg/kg, and diazepam 0.1 mg/kg orally 90 minutes before the induction of anesthesia. Anesthesia was induced with oxygen, nitrous oxide, and halothane by mask and maintained with fentanyl (15 μg/kg) and halothane (0.25–1.0%). Ventilation was controlled and neuromuscular blockade was maintained using incremental doses of pancuronium. Pulse rate, blood pressure, Sao$_2$ (90–95%), and central venous pressure remained stable during skin incision and sternotomy. During dissection of the aorta and placement of the arterial cannula of the bypass circuit, blood pressure increased to 135/100

mm Hg and was accompanied by an increase in heart rate and a marked reduction in Sao$_2$ to 75%. Epicardial echocardiography and CFI demonstrated a net right-to-left shunt at the site of the VSD, as in Case 1. Increased sympathetic tone due to a light plane of anesthesia with a secondary hypoxemic spell because of an increase in dynamic right ventricular outflow tract obstruction was suspected. Propranolol (0.25 mg) was immediately administered IV and the halothane concentration was increased. Sao$_2$ gradually increased to 95%, systemic arterial pressure decreased to 90/58 mm Hg, and heart rate decreased to 125 beats/min. During these maneuvers epicardial echocardiography with CFI showed a reversal of shunting with a net left-to-right ventricular shunt. The remainder of the anesthetic and operative course proceeded uneventfully.
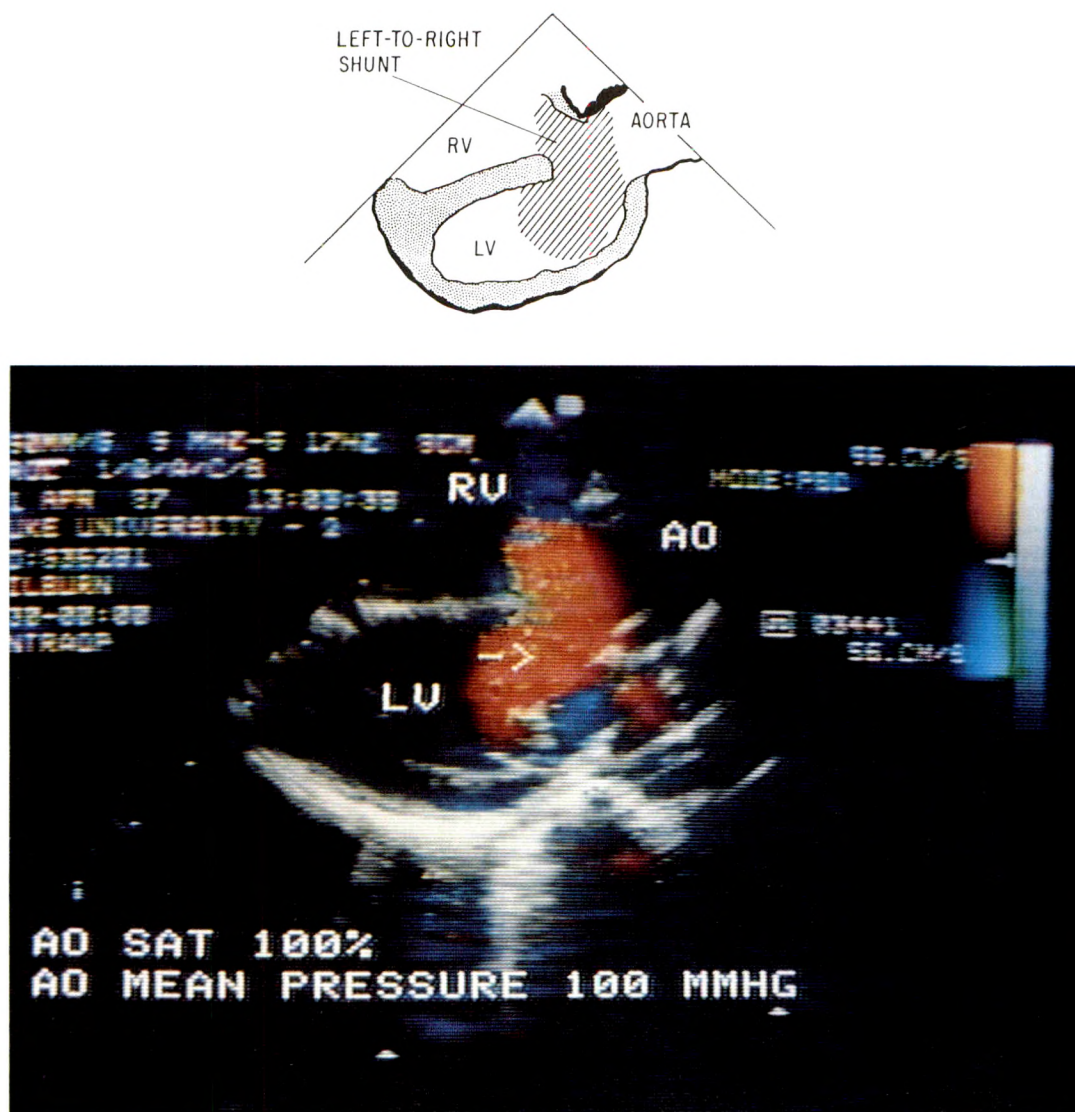
Figure 2. Doppler color flow map (left) and schematic diagram (right) of a modified long axis view illustrating left-to-right shunting (red jet) across the ventricular septal defect during systole.

Echocardiographic Methodology and Results

As part of a routine approach to the intraoperative assessment of congenital heart defects at our institution, epicardial echocardiography with CFI was performed at specific intervals in these two patients. A 5.0-MHz short-focus transducer was used and connected to a Hewlett-Packard echocardiograph (77020 CF) incorporating a color-imaging module. In each patient the transducer was topically sterilized and then passed into the operative field where it was ensheathed in a sterile plastic sleeve before epicardial use. This phased array transducer, containing 64 elements, provided high-resolution black and white images recorded from the epicardial surface and displayed on a video screen. The same ultrasound transducer was used simultaneously for color flow imaging.

Color flow imaging is accomplished by electronically separating the reflected ultrasound waves into those defining anatomic targets and those defining flow within the chambers (5). Images of flow are created when sound waves are reflected from moving red blood cells and provide blood flow information, recorded in color. Therefore, cardiac structures are displayed in a monochrome mode, whereas blood flow velocity is presented in color. Using CFI the entire cardiac image can be scanned along several lines of sight within the sector arc of the two-dimensional echocardiographic image. Because blood flow toward and away from the transducer have different Doppler frequency shifts, direction of blood flow can be identified and assigned specific colors. By convention, blood flowing away from the transducer is shown in blue, and flow toward the transducer is

red (Figs. 1, 2). The magnitude of the flow velocity is indicated by the brightness of color and turbulence, representing varying velocities of blood, and appears as a mosaic pattern of color.

In Case One with the transducer positioned on the epicardial surface, systolic flow through the ventricular septal defect is seen as a blue jet indicating flow away from the transducer (Fig. 1). This represents flow from the right ventricle to the left ventricle, i.e., a net right-to-left shunt associated with hypotension and systemic oxygen desaturation. Immediately after phenylephrine was administered to the patient in Case One, continuous two-dimensional echocardiography with CFI demonstrated reversal of shunt flow (Fig. 2). In Figure 2, blood flow direction through the VSD now appears as a red hue, indicating flow toward the transducer with flow directed from the left ventricle to the right ventricle. This change in shunting to a left-to-right shunt was associated with increases in blood pressure and Sao_2. Not shown, similar changes in shunting before and after propranolol were observed in Case Two by CFI.

Discussion

Patients with cyanotic congenital heart disease undergoing surgical procedures are at risk for worsening right-to-left shunting and for developing hypoxemia. This is especially true in patients with tetralogy of Fallot where the interventricular communication, i.e., VSD, is large and nonrestrictive, and where the relative resistances of the pulmonary and systemic outflow tracts and vascular beds are the major determinant of shunt flow (4). In these patients, a decrease in systemic vascular resistance and/or an increase in right ventricular outflow tract obstruction due to sympathetic stimulation produces an increase in right-to-left shunting and a decrease in Sao_2. These changes have been suggested as mechanisms for the production of hypoxemic or "tet" spells (5).

The treatment of the hypoxemic spells has been directed at increasing systemic vascular resistance using an α-receptor agonist, decreasing dynamic right ventricular outflow tract obstruction using β-adrenergic blockade, controlling respiratory drive and hyperpnea with morphine, and correcting any metabolic acidosis using sodium bicarbonate. Phenylephrine or propranolol have been effective in relieving these hypoxemic spells and are the current methods of treatment (6,7). Phenylephrine or propranolol are preferred for the intraoperative management of hypercyanotic spells because of their ease of administration, rapidity in onset of correcting the hemody-

namic alterations, and low incidence of side effects (2). Although certain dynamics of the relief of hypoxemic spells are known, the precise demonstration of shunting and the precise pharmacologic effects on shunting have not been demonstrated.

We report two cases of intraoperative hypoxemic spells in patients with tetralogy of Fallot in whom two-dimensional echocardiography with CFI was used to document blood flow patterns before, during, and after therapeutic interventions. In Case One, the hypoxemic spell was a direct result of hypotension where a decrease in systemic vascular resistance augmented right-to-left shunting and a fall in Sao_2. The administration of phenylephrine to this patient immediately improved Sao_2 by increasing systemic arterial pressure and, presumably, systemic vascular resistance, with a resultant increase in pulmonary blood flow. In Case Two, the hypoxemic episode was a result of a light plane of anesthesia where surgical stress increased sympathetic tone and dynamic right ventricular outflow tract obstruction, augmenting right-to-left shunting and causing a decrease in systemic oxygen saturation. The administration of propranolol and deepening the level of anesthesia immediately increased systemic arterial saturation by reducing right ventricular outflow tract obstruction with β-adrenergic blockade and decreasing sympathetic tone, augmenting pulmonary blood flow. In both cases, we observed net right-to-left shunting through the VSD associated with systemic arterial oxygen desaturation by two-dimensional echocardiography with CFI. Furthermore, after therapeutic interventions, shunt reversal, i.e., net left-to-right shunting, was demonstrated and was associated with improvements in Sao_2. Several mechanisms for such changes in shunting relating to the pharmacologic manipulation of the relative resistances of the systemic vascular bed and the right ventricular outflow tract have been suggested but never demonstrated. Heretofore speculated, we directly observed the results of these manipulations on the direction and extent of shunting.

Doppler CFI is a method for imaging blood flow through the heart by displaying flow data on the two-dimensional echocardiographic image (8,9). Using this technology the characteristics of blood flow, i.e., direction, velocity, and size, are displayed on the cardiac image by means of color encoding of the Doppler-generated flow signal. The intraoperative use of CFI has recently been reported using a transesophageal approach (10). In the cases reported here the color flow images recorded from the epicardial surface of the heart provided immediate information about blood flow direction that permitted specific

therapeutic interventions and an assessment of therapy.

In conclusion, the present case reports offer the first direct evidence of net right-to-left shunting during a hypoxemic episode (tet spell) where shunt reversal and augmented systemic oxygen saturation were observed after therapeutic interventions. These findings support the hypothesis that an increase in systemic vascular resistance relative to right ventricular outflow obstruction augments pulmonary blood flow and relieves hypoxemic spells. The pharmacologic effects of phenylephrine and propranolol account for the changes in shunt reversal observed. The use of two-dimensional echocardiography with CFI provided a reliable method of assessing these changes in intracardiac blood flow.

References

1. Rudolph AM. Congenital Diseases of the Heart. Chicago: Year Book, 1974:401–28.

2. Hickey PR, Wessel D. Treatment of Congenital Heart Disease. In: Kaplan JA, ed. Cardiac anesthesia. New York: Grune & Stratton, 1987:625–723.

3. Kisslo J, Adams D, Belken RN. Doppler color flow imaging. New York: Churchhill Livingstone, 1988.

4. Berman W Jr. The hemodynamics of shunts in congenital heart disease. In: Johansen KM, Burggren WW. Cardiovascular shunts: phylogenetic, ontogenetic, and clinical aspects. New York: Raven Press, 1985:399–410.

5. Honey M, Chamberlain DA, Howard H. The effect of beta-sympathetic blockade on arterial oxygen saturation in Fallot's tetralogy. Circulation 1964;30:501–10.

6. Nudel DB, Berman MA, Talner NS. Effects of acutely increasing systemic vascular resistance on oxygen tension in tetralogy of Fallot. Pediatrics 1976;58:248–51.

7. Ponce FE, Williams LC, Webb HM, Riopel DA, Hohn AR. Propranolol palliation of tetralogy of fallot: experience with long-term drug treatment in pediatric patients. Pediatrics 1973; 52:100–8.

8. Sahn DJ. Real-time two-dimensional Doppler echocardiographic flow mapping. Circulation 1985;71:849–53.

9. Omoto R. Color atlas of real-time two dimensional doppler echocardiography. Tokyo: Shindan-To-Chinyo Co. Ltd., 1984.

10. de Bruijn NP, Clements FM, Kisslo JA. Intraoperative transesophageal color flow mapping: initial experience. Anesth Analg 1987;66:386–90.

Transient Right-Left Interatrial Shunt during Emergence from Anesthesia: Demonstration by Color Flow Doppler Mapping

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and John C. Powell, MD

Key Words: HEART, CONGENITAL DEFECTS—foramen ovale. ANESTHESIA—pediatric.

Transient arterial hypoxemia can occur during emergence from anesthesia, especially when patients react to the endotracheal tube with coughing, forced exhalation, and breath-holding. Unless there is a real-time technique of imaging the cardiac chambers, it is difficult to document an acute and transient right-to-left (R-L) intracardiac shunt as a cause of arterial hypoxemia. Color flow Doppler mapping (Diasonics CFM. model 700 Sweden) provides such a possibility.

Case Report

A 2-month-old 4.5 kg white female (ASA class I) was scheduled for elective bilateral inguinal herniorrhaphy. Physical examination revealed a normally active healthy child with no cardiovascular or pulmonary abnormality. Anesthesia was induced intravenously with thiopental (25 mg IV) followed by succinylcholine 10 mg IV for muscle relaxation to facilitate tracheal intubation. After tracheal intubation with 3.5 mm (ID), uncuffed plastic tube anesthesia was maintained with isoflurane, nitrous oxide, and oxygen. Ventilation of the lungs was controlled and end-tidal CO_2 was monitored. At the conclusion of surgery, during the breathing of 100% oxygen, the oxygen saturation was noted by pulse oximetry to rapidly decrease from 100 to 50% during a period of breath-holding while reacting to the endotracheal tube. The

patient's lungs were hyperventilated with oxygen and isoflurane was readministered. A color flow Doppler probe was then placed over the subcostal region so as to visualize the cardiac chambers, and isoflurane was discontinued.

The patient again began to react to the endotracheal tube spontaneously, and the oxygen saturation again rapidly decreased from 100 to 50%. The color-Doppler demonstrated a patent foramen ovale with a small left-to-right (L-R) intracardiac shunt initially followed by more marked right-to-left (R-L) shunting at the atrial levels (Fig. 1). Continued ventilation of the lungs with oxygen resulted in oxygen saturation returning to 100%, and at this time, no shunt could be demonstrated while the patient was coughing but not bearing down on the tracheal tube. Then tracheal extubation was done.

Discussion

Acute arterial hypoxemia from a transient right-to-left shunt through patent foramen ovale has been described (1). However, because of the transient nature of this phenomenon, it is difficult to do a systematic study. In 7 of 35 infants and children, we observed transient severe hypoxemia (decreased saturation of hemoglobin with oxygen as reflected by pulse oximetry) during emergence from anesthesia during bearing down due to continued presence of the tracheal tube (2).

Color flow Doppler mapping provides useful technology for a real time demonstration of cardiac imaging. Doppler color flow mapping is a two-dimensional echocardiogram using advanced electronics for color flow imaging. The information from the ultrasound pulses is separated into amplitude (imaging) and velocity (Doppler shift) (3). Higher amplitude signals from the intracavitary walls and valves are
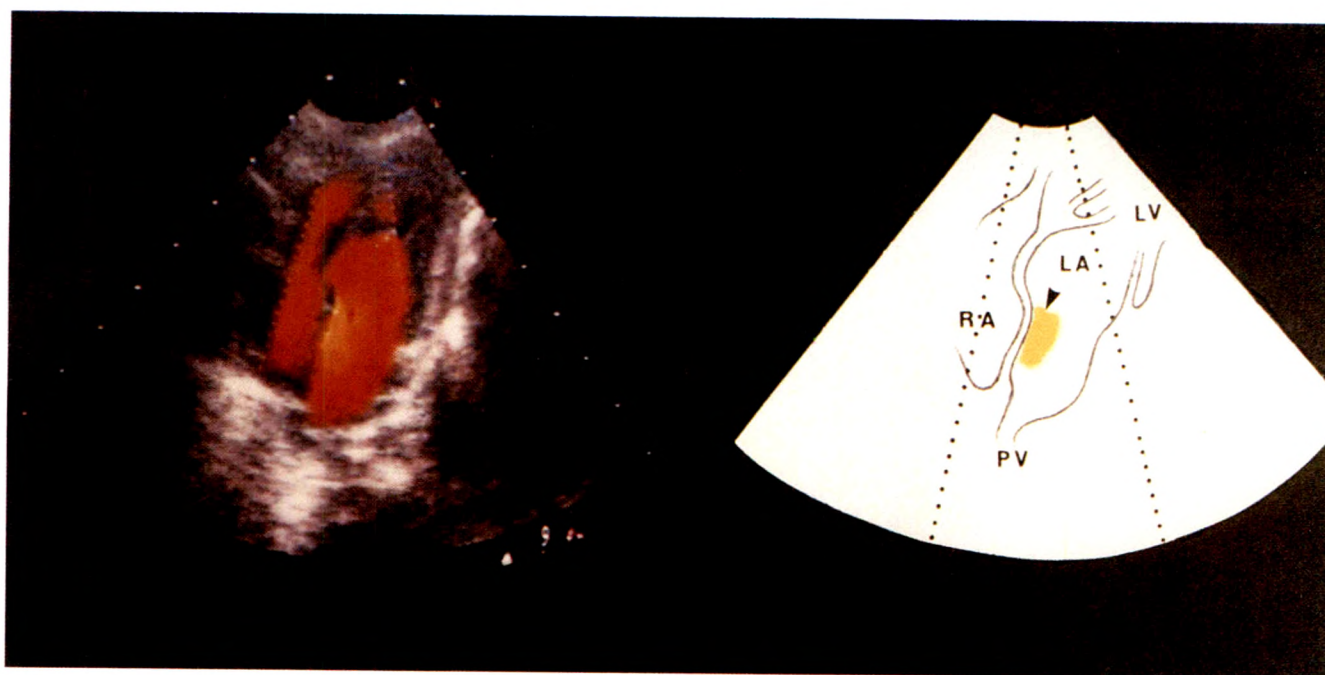
Figure 1. Color flow Doppler obtained during bearing down on the endotracheal tube shows R-L shunt at the atrial level (**yellow color area**). The line diagram, drawn for clarity, indicates the position of the right atrium (RA), left atrium (LA), and the arrow for the R-L shunt. LV = left ventricle; PV = pulmonary vein.

recorded with digital color coding (red [positive] toward transducer and blue [negative] away from transducer). With the use of parasternal axis mitral, aortic and pulmonary valve dysfunction can be detected. A four chamber view helps detect intracardiac shunts.

During emergence from anesthesia, children often cough and initially bear down on the tracheal tube with exhalation. This results in decreased lung volumes. Difficulty in positive pressure ventilation of the lungs leading to hypoventilation can occur. Decreased lung volumes and hypoventilation with respiratory acidemia lead to increased pulmonary vascular resistance and right atrial pressure with development of a R-L shunt in the presence of a patent foramen ovale. The initial presence of a small L-R shunt followed by the R-L shunt and later absence of a shunt indicates a foramen ovale. Though commonly a R-L shunt occurs alone, a small L-R shunt can occur in some patients with changes in the competence of the valve of the foramen due to distension of atrial chambers (4). With the use of a Valsalva maneuver, for example, R-L shunt was demonstrated in 18% of adults during the release phase of Valsalva (5).

R-L shunt at the atrial level occurs with reaction to the tracheal tube during emergence from anesthesia. The mechanism of increase in right atrial pressure associated with reaction to the tracheal tube is dif-

ferent than it is during a Valsalva maneuver. During the former, it is the change in the lung volumes that contributes to increased right atrial pressure. During a Valsalva maneuver, changes in intrathoracic pressure contribute to the hemodynamic changes.

The incidence of patent foramen ovale is higher in the earlier years of life (35%) (6). When present, the development of a R-L shunt is, thus, more frequent in children. Though transient, this type of R-L may have important clinical implications. Hypoxemia as well as paradoxical systemic air or particulate emboli can occur during the period of bearing down on the tracheal tube during recovery from general anesthesia in children.

In summary, we describe a non-invasive real time color flow Doppler detection of a transient R-L shunt at the atrial level during reaction on the endotracheal tube associated with emergence from anesthesia in a child. Such R-L shunt can and did result in transient arterial hypoxemia and a potential for paradoxical systemic embolism. We recommend continued ventilation of the lungs with 100% oxygen during the period of bearing down on the tracheal tube to correct hypoxemia and then only remove the tracheal tube.

References

1. Moorthy SS, Dierdorf SF, Krishna G, Caldwell RL, Alcorn DM. Transient hypoxemia from a transient right-to-left shunt in a child during emergence from anesthesia. Anesthesiology 1987; 66:234-5.

2. Moorthy SS, Dierdorf SF, Krishna G. Transient hypoxemia during emergence from anesthesia in children. Anesthesiology Review 1988;15:20-3.

3. Duncan WJ. Color Doppler in Clinical Cardiology. Philadelphia: WB Saunders, 1988:3-12.

4. Schroeckenstein RF, Wasenda GJ, Edwards JE. Valvular competent foramen ovale in adults. Minn Med 1972;55:11-3.

5. Lynch John J, Schuchard GH, Gross CM, Wann LS. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva Maneuver contrast echocardiography. Am J Cardiol 1984;53:1478-80.

6. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;39:17-20.

Letters to the Editor

Value of Heart-Synchronized Ventilation during Extracorporeal Shock Wave Lithotripsy Remains Unproven

To the Editor:

We read with interest the clinical report by Jansson et al., "Heart-Synchronized Ventilation during General Anesthesia for Extracorporeal Shock Wave Lithotripsy" (1). However, we find that their conclusion that timing the respirations to the heart rate decreases the movement of stones is based, in part, on a control group in which there were variables not present in the study group.

When conventional ventilation was compared with heart-synchronized ventilation, mean stone movements were 18.5 mm and 2.8 mm in the nonoperated group. In the operated group, mean movement was 13.8 mm with conventional ventilation and 3.1 mm with heart-synchronized ventilation. However, heart synchronization was not the only variable. In fact, we find three variables: heart synchronization of ventilation, ventilatory tidal volume, and ventilatory rate. To assess the effects of heart-synchronized ventilation only upon stone movement, tidal volume and ventilatory rate must be the same in both groups.

Ventilatory rate was 12 per minute with conventional and 69 per minute with synchronized ventilation. Since tidal volumes were not listed, they can only be estimated from the data that are given in the report. Conventional ventilation of 4.5 liters/m²/min would produce a tidal volume of .675 liters [(4.5 × 1.8) ÷ 12]. Heart-synchronized ventilation at a rate of 69 per minute with a minute ventilation of 13.3 L/min would be accompanied by an average tidal volume of .192 liters (13.3 ÷ 69). Accounting for compressible volume would further increase the proportional disparity.

From the data supplied in the study, one could easily conclude that significant reduction of tidal volume results in a significant reduction in stone movement. It is necessary to use identical tidal volumes and respiratory rates, triggered by heart rate and at random, while comparing total

shocks necessary to break similarly-sized stones, in order to prove the authors' conclusions.

While we agree that coupling mechanical respirations to ECG may decrease movement of stones and hence promote more efficient ESWLs, the report by Jansson et al., leaves the theory unproven.

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References

1. Jansson L, Bengtsson M, Carlsson C. Heart-synchronized ventilation during general anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1988;67:706–9.

Bier Block Tourniquet Pressure

To the Editor:

In 1908, Bier described a method of analgesia produced by emptying veins of blood and then filling them with local anesthetic solution held in place by a tourniquet (TQ) (1). Holmes revived interest in this technique in a 1963 publication (2) in which the use of two tourniquets was described. The recent trend toward outpatient anesthesia has caused many clinicians to favor this "Bier block" over brachial plexus block for hand surgery, since recovery to meet discharge criteria is usually more rapid with the former.

For success, the TQ pressure to retain the local anesthetic must of course exceed venous pressure. It must also be above arterial pressure if surgical bleeding is to be avoided and anesthetic agent trapped in the veins is not to be diluted by blood entering from the arteries. Since the double TQ technique mandates use of narrow cuffs, well known to require higher pressures to occlude arteries, it is important to known how high to inflate such a cuff. This was recognized by Davies and colleagues (3) who studied 20 patients with a Hoyle double cuff TQ and a Dinamap Model 845 blood pressure recorder, comparing the pressures required to prevent palpation of the radial pulse.

Table 1. Differences Between Systolic (SP) and Pulse Occlusion (POP) Pressures in Volunteers with One or Two TQ Cuffs Inflated

Subject	Arm Size, cm	SP range mmHg	2 cuffs (POP)-(SP) mmHg	1 cuff (POP)-(SP) mmHg
1	25	100-107	55	103
2	27	112-116	33	62
3	28	115-136	39	110
4	29	124-130	51	49
5	29	112-120	30	85
6	30	107-112	92	128
7	31	116-131	29	56
8	36	120-128	67	95
Means			49.5	86.0
± SD			21.8	28.2

Their "occlusion pressure," measured with the double cuff device, was from 3 to 120 mm Hg higher than the systolic BP derived from the Dinamap device. They concluded by recommending that the occlusion pressure, determined with the narrow cuff of the Hoyle device, be determined for each patient and that this cuff then be inflated to a value 100 mm Hg higher than this, to allow for rises of BP intraoperatively. A recent letter by Worth and Kirk (4) suggests a similar strategy by determining the pressure necessary to halt pulse signals from a pulse oximeter sensor placed on a finger of the operative arm, then inflating the TQ to a value 50 to 100 mm Hg higher.

We wished to verify the observation of Davies et al. (3) that systolic BP is poorly correlated with pulse occlusion pressure, using the more objective method of Worth and Kirk (4) to determine the latter. Using ourselves and six colleagues as subjects, the following measurements were made: BP was taken with an Infrasonde D-4000, (Puritan-Bennett), then that cuff was replaced with a 45.7 cm TQ with two 4.8 cm wide cuffs attached to an A.T.S. 500 tourniquet system (Aspen Labs), an adult digit oxygen transducer (Nellcor DS-100A) was placed on the index finger and connected to a Nellcor N-100 oximeter unit, and both cuffs were inflated incrementally until the pulse display disappeared. The pressure was maintained for about a minute to be sure the oximeter did not reset itself and begin again to display pulsation. The TQ was then released, the cuff removed and replaced by that of the Infrasonde unit, the BP again determined, the cuff removed and replaced by the double cuff, and the pulse occlusion pressure determined with only one of the two cuffs inflated incrementally. The differences between systolic (SP) and pulse occlusion (POP) pressures were calculated for each pair of pressures and recorded, as was the arm circumference measured at mid-humerus.

The results are given in Table 1. The systolic pressure ranges of these subjects, including values obtained before, during and after the POP measurements, fall within normal ranges. The POP determined with two cuffs inflated range from 29 to 92 mm Hg higher than SP, and when only one cuff of the same device was inflated, from 49 to 128 mm Hg higher. The only exception to this was subject four, who had essentially the same increase of POP, whether one or

two TQ cuffs were inflated. There was no relationship of arm size to these differences between POP and SP.

We conclude that commonly used guidelines for TQ inflation that are based on an arbitrary increment above systolic BP may markedly under- or overestimate the pressure needed to stop digital arterial pulsation. We suggest that the method of Worth and Kirk (4) has merit, except for their suggestion of an increment of 50 to 100 mm Hg higher than occlusion pressure. We favor the higher figure, 100 mm Hg above the POP determined with one cuff inflated, as suggested by Davies (3).

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References

1. Bier A. Ueber einen neuen Weg Localanasthesie an den Gliedmaassen zu erzeugen. Arch Klin Chir 1908;86:1007-1016.

2. Holmes C McK. Intravenous regional analgesia. A useful method of producing analgesia of the limbs. Lancet 1963;1:245-247.

3. Davies JAH, Hall ID, Wilkey AD, Smith JE, Walford AJ, Kale VR. Intravenous regional analgesia. The danger of the congested arm and the value of occlusion pressure. Anaesthesia 1983;39:416-421.

4. Worth ER, Kirk WO. Cessation of blood flow in intravenous regional anesthesia. Anesth Analg 1988;67:1020.

Breathing-Circuit Stethoscope and Circuit Disconnection

To the Editor:

We were interested in the letter from Kainuma and Shimada (1) describing a breathing-circuit stethoscope and the subsequent comments by Gravenstein (2) warning of the hazards of one more connection in the breathing circuit as well as the potential for endotracheal tube dislodgement.

Being particularly concerned about the efficacy of this device in detecting intra-operative disconnection between the endotracheal tube (ETT) and the ETT corrugated adapter, we tested the ability of both experienced and junior anesthesiologists to detect such a disconnect in the operating room.

A breathing-circuit stethoscope modelled precisely on the device of Kainuma and Shimada was assembled using a National Catheter Corporation esophageal catheter (size 18Fr) attached to a monaural stethoscope and incorporated into a circle breathing system. All patients in the study were having endotracheal anesthesia using controlled ventilation and a volume-cycled gas-driven ventilator (Campbell Ventilator, Ulco Engineering Pty Ltd). Patients were monitored according to the requirements of their particular procedure, including pulse oximetry in all cases. All tests were made during a stable period in the operation and no attempt was made to influence ambient noise or general activity in the operating room.

Six faculty members and four experienced anesthesia residents took part in the evaluation. All were blind to the

integrity or otherwise of the breathing circuit. Each anesthesiologist was shown the nature of the device then asked to connect a monaural stethoscope and appraise the effectiveness of the arrangement. During a brief discussion, with verbal pauses lasting several patient breaths, the anesthesiologists were asked their opinion of the device without any indication that a deliberate disconnection was about to take place.

At some time in this period the circuit disconnect alarm was deactivated, the ETT disconnected from the circuit, and the corrugated connector moved sideways under the patient blanket to simulate inadvertent disconnection under drapes. This condition was maintained for three consecutive cycles of the ventilator. The circuit was then re-connected and the circuit disconnect alarm re-activated. All disconnections lasted no more than 20 seconds and no patient experienced any significant deterioration in oxygen saturation.

At the completion of these maneuvers the anesthesiologists were asked to remove the stethoscope and were questioned on the quality of breath sounds that had been heard and any general impressions of the device. Next they were told that a deliberate disconnection had occurred and they were asked to identify at which time and for how many breaths such disconnection had lasted. Without exception no individual was able to recognize the surreptitious disconnection nor the period for which it lasted.

While there is potential merit in having remotely monitored breath sounds as described in the original communication by Kainuma and Shimada, we believe that the risk of missing an inadvertent circuit disconnect substantially outweighs the advantages.

Circuit disconnects are one of the most common critical incidents leading to potential intra-operative morbidity (3). In the noisy environment of the operating room it may be extremely difficult to discern by a monaural stethoscope that a qualitative change in conducted breath sounds has occurred. It also appears that much of the conducted "breath sounds" of the breathing-circuit stethoscope are caused by inspiratory and expiratory gas movement in the breathing circuit itself rather than being conducted from the patient's airways. The use of a volume-cycled ventilator may give no ventilatory clues that a disconnect has occurred, and partial disconnects may not trigger some circuit disconnect alarms.

We believe that the breathing-circuit stethoscope could provide an unreliable and dangerously false sense of security. It also appears to be an inappropriate source for monitoring patient breath sounds which are more appropriately determined by classical stethoscopy at pre-cordial, pre-tracheal or esophageal sites.

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References

1. Kainuma M, Shimada Y. A breathing circuit stethoscope for continuous monitoring of breath sounds. Anesth Analg 1987;66:1057–8.

2. Gravenstein N. Use of breathing circuit stethoscopes can have complications. Anesth Analg 1988;67:421.

3. Cooper JB, Newbower RS, Long CD, et al. Preventable anesthesia mishaps—a study of human factors. Anesthesiology 1978;43:399–406.

Isoflurane: Myocardial Ischemia without Coronary Steal?

To the Editor:

An excellent study by Khambatta et al. (1) elegantly confirmed that, first, isoflurane dilates coronary vessels (2,3), second, in case of coronary stenosis isoflurane may cause redistribution of coronary blood flow between ischemic and non-ischemic areas (4); third, and most important, isoflurane can actually induce myocardial ischemia in patients with coronary artery disease (2). Contrary to the authors' conclusion, however, the study did not suggest that coronary steal was responsible for isoflurane-induced myocardial ischemia. First, coronary outflow from the region supplied by the obstructed left anterior descending coronary artery was practically the same in both the isoflurane and halothane groups. Great cardiac vein blood flow was 44 ± 5 ml/min in the halothane group and 56 ± 6 ml/min in the isoflurane group. Second, oxygen consumption in this area was 5 ± 0.4 ml/min in both groups despite the fact that global coronary flow increased with isoflurane and decreased with halothane. In addition, the extent of reduction in global myocardial lactate extraction during isoflurane anesthesia may indicate a deterioration in the balance between energy production and use outside the region supplied by the obstructed coronary artery. If isoflurane, which is a coronary vasodilator, and halothane, which does not have a coronarodilating property, provide the same coronary flow in the area supplied by the constricted artery, coronary steal cannot explain why isoflurane, in contrast to halothane, causes ischemia.

Isoflurane may cause or contribute to the ischemia by a direct inhibition of the electron transport chain in mitochondria at the level of NADH dehydrogenase. The difference between halothane and isoflurane in this regard is rather impressive: at the concentrations producing equal negative inotropic effect, isoflurane inhibits the electron transport chain in the myocardium, and thus energy production, three times as much as halothane (5). The effect of halothane on the balance between energy production and utilization in the hypoperfused myocardium (as reflected by NADH level) may even be beneficial (6). We suggest that in case of isoflurane the detrimental effect on the balance between energy production and utilization is such that this anesthetic may produce myocardial ischemia without coronary steal.

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References

1. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 1988;67:936–42.

2. Reiz S, Balfors E, Sorensen MB, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.

3. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984;63:557–65.

4. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.

5. Kissin I, Altman DF, Smith LR. Effects of volatile anesthetics on myocardial oxidation-reduction status assessed by NADH fluorometry. Anesthesiology 1983;59:447–52.

6. Kissin I, Thomson CT, Smith LR. Effect of halothane on contractile function of ischemic myocardium. J Cardiovasc Pharmacol 1983;5:438–42.

In Response:

We thank Drs. Kissin and Gelman for their interest in our paper (1). We are indeed pleased that they agree with our conclusions, which are that, in the presence of coronary stenosis, isoflurane induces coronary vasodilation redistribution of coronary blood flow, and myocardial ischemia.

When myocardial ischemia occurs, coronary sinus drainage is comprised of an admixture of blood from both ischemic and nonischemic regions. Even within the great cardiac vein, which drains the region supplied by the left anterior descending coronary artery, one may find blood emanating from hypoperfused subregions and regions that have undergone luxury perfusion. Perfusion of an ischemic area is thus independent of the total coronary blood flow.

The blood supply to a region perfused by a stenotic coronary artery is augmented by collateral vessels which preserve myocardial viability. When coronary steal occurs, this fine balance is interrupted and myocardial ischemia results (2). Buffington and his associates have shown that a quarter of the patients for coronary artery bypass surgery have a coronary steal-prone anatomy and that the incidence increases with the patient's age and history of previous infarction (3). We observed a similar incidence of ischemia in our patients.

In summary, we have shown that both myocardial ischemia and coronary steal occurred simultaneously; although inhibition of the electron transport chain in mitochondria by isoflurane is an interesting concept (4), there is an old adage, "If you hear hoof beats, don't think zebras."

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References

1. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 1988;67:936–942.

2. Becker LD. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57:1103–1110.

3. Buffington CW, Davis KB, Gillispie BS, Pettinger M. The prevalence of steal-prone coronary anatomy in patients with coronary artery disease:

An analysis of the coronary artery surgery study registery. Anesthesiology 1988;69:721–727.

4. Kissin I, Altman DF, Smith LR. Effects of volatile anesthetics on myocardial oxidation-reduction status assessed by NADH fluorometry. Anesthesiology 1983;59:447–452.

Soft and Firm Introducers for Translaryngeal Guided Intubation

To the Editor:

Dr. Freund and colleagues (1) reported a case of difficult endotracheal intubation solved by employing a translaryngeally inserted epidural catheter which was subsequently threaded through a Eschmann stylet (with its woven ends cut off). The endotracheal tube was then slid over the Eschmann stylet into the trachea.

We described a technique employing a pair of introducers, soft and firm, to accomplish the same purpose some time ago (2,3). The only differences between our technique and that described by Freund et al. are that we used a smaller needle/catheter (20Ga vs 17Ga) and a spring wire with its plastic sheath protector. The spring wire is stiffer than the epidural catheter, and is, therefore, much easier to pass through the vocal cords. The sheath protector which comes with wire has to be shortened only at the distal end. This avoids the possibility of trauma from the rough cut end of the Eschmann stylet.

Endotracheal intubation guided by a translaryngeally inserted introducer is traditionally referred to as "retrograde intubation." However, since the endotracheal tube is not inserted from below the vocal cords, though the guide wire is, it has been suggested that it would be more appropriate to call it "translaryngeal guided intubation" (TLI) (4).

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References

1. Freund PR, Rooke A, Schmid H: Retrograde intubation with a modified Eschmann stylet. Anesth Analg 1988;67:605–6.

2. King HK: Translaryngeal guided intubation using a sheath stylet. Anesthesiology 1985;63:567.

3. King HK, Wang LF, Khan AK, Wooten DJ: Translaryngeal guided intubation for difficult intubation. Crit Care Med 1987;15:869–71.

4. King HK: Translaryngeal guided intubation. Anesth Analg 1985;64:650–1.

Edrophonium and Pralidoxime

To the Editor:

Recent advertisements in this journal for the Reversol® brand of edrophonium are misleadingly unclear. The manufacturer states that the action of the drug "is due primarily

to the inhibition or inactivation of acetylcholinesterase" and recommended that "pralidoxime chloride (a cholinesterase reactivator)" may be used in conjunction with atropine for treatment of overdosage.

Of the drugs routinely employed clinically for the specific inhibition of acetylcholinesterase, edrophonium is unique in lacking a transferable ester group. Thus, edrophonium inhibits acetylcholinesterase through noncovalent binding but does not inactivate the enzyme in the sense that the term inactivation is generally applied to enzymes (1). In contrast, carbamate esters (such as neostigmine) and phosphorus-containing esters (such as echothiophate) inactivate acetylcholinesterase through covalent modification of the protein in transesterification reactions (2,3). Pralidoxime reactivates acetylcholinesterase by functioning as an acceptor in a subsequent transesterification (2,3). Thus, pralidoxime cannot increase the activity of acetylcholinesterase inhibited by edrophonium. In theory, pralidoxime could worsen cholinergic crisis caused purely by edrophonium since pralidoxime has some low-grade activity as a reversible inhibitor of acetylcholinesterase (4). As the advertisement is intended to indicate, pralidoxime has a rationale for treatment of edrophonium-provoked cholinergic crisis only in the additional presence of an ester-type inactivator of cholinesterase.

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References

1. Walsh CT. Suicide substrates, mechanism-based enzyme inactivators: recent developments. Ann Rev Biochem 1984;53:493-535.
2. Wilson IB, Ginsburg S. A powerful reactivator of alkylphosphate-inhibited acetylcholinesterase. Biochim Biophys Acta 1955;18:168-170.
3. Kitz RJ, Wilson IB. Esters of methanesulfonic acid as irreversible inhibitors of acetylcholinesterase. J Biol Chem 1962;237:3245-3249.
4. Mounter LA, Ellin RJ. The inhibition of acetylcholinesterase by 2-pyridinealdoxime methyl halide. Mol Pharmacol 1968;4:452-456.

In Response:

We wish to take issue with Dr. Alston's comment that our "advertisements" for the Reversol brand of edrophonium chloride are "misleadingly unclear." The advertisement in question is simply an announcement of the availability of edrophonium chloride from Organon. Dr. Alston's comments appear to refer to the accompanying prescribing information which appears on the reverse side of the announcement.

In accordance with FDA regulations this prescribing information contains virtually the same language as that of the pioneer edrophonium chloride product. However, it is Organon's understanding that the FDA is currently reviewing labeling for all edrophonium chloride products. We will bring Dr. Alston's incisive comments to the attention of the FDA.

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Book Reviews

Anyone Can Intubate

Christine E. Whitten. San Diego: Medical Arts Press, 1989, 150 pp, $14.95.

Anyone Can Intubate is a simplistic, economical illustrated guide to intubation. The intended audience is medical and nursing students, paramedics and anesthesia residents. The author presents her subject in a basic straightforward manner in the anesthetic vernacular and in an amusing tone. The 11 concise chapters include anatomy, airway evaluation, equipment, oral and nasal technique in adults as well as intubation in children, test for tube placement, common errors in technique, "tricks of the trade," and seven pages of complications "during and after intubation." Each chapter includes references.

The only shortcoming, but not a serious drawback, is the absence of any photographs. The hand-drawn illustrations adequately convey the message. While this book will probably not be placed alongside any "bibles of anesthesia," it fulfills the subtitle "a practical, step-by-step guide for the health profession." This unpretentious little book provides an excellent overview for the neophyte and can be read in an evening.

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Computing for Clinicians

T. Chart. Bristol, UK: IOP Publishing Ltd., 1988, 136 pp, $32.40.

Computing for Clinicians is intended for the physician who has little or no knowledge of computing. The book's assets are that it is relatively short and follows a tightly structured outline of pertinent topics. It discusses both the administrative and clinical aspects of computing. It also introduces many of the basic concepts of computing at the beginner level. A short book of this sort is needed, and in many aspects, this book meets those needs.

Certainly, the group of physicians and medical personnel for whom this book is targeted is in need of such a book. However, nowhere in this book does the author transmit the youthful excitement that people can experience with computing once they have overcome their initial fears of the technology. The tone of this book is that computing is a necessary burden for our profession, imposed on us in order to increase our efficiency. This may reflect the author's choice of operating systems. He learned computing on "command line" operating systems such as MS DOS. Though this type of operating system is the most common, the trend is to support graphic interfaces on all computers, and the first moments of computer interaction may decide whether a person is going to enjoy or resist further learning.

Graphic interfaces such as the Macintosh operating system, NeWs, etc., in combination with pointing devices such as the "mouse," track balls, or pen-style pointers enhance the crucial first experience. Despite this, the author discredits the utility of pointer devices early in his book. He feels that users always return to the keyboard and that other devices are therefore relatively useless. This book was, however, written in the United Kingdom, which may explain the author's viewpoint. In this country, graphic interfaces using pointer devices provide the intimidated user with an environment which quickly becomes an indispensable tool, and keyboard equivalents are discovered gradually by the user, after the initial fears and confusions are overcome. Even visual effects often used in such software may heighten the user's interest and desire to learn.

Another opinion stated by the author is that there is no reason for a clinician to understand anything more about certain technical aspects than the simplified definitions which he gives in his book. It may be unnecessary and even destructive to insist that a new user be capable of handling technical jargon from the outset, but the book should acknowledge that many readers will get involved and desire greater understanding. Technical understanding allows the physician to solve problems better as she/he becomes more sophisticated. Technical expertise may be separate from the ability to use, but some clinicians benefit from understanding what is being done to the information in the computer, especially the clinician who intends to manage a practice or perform research.

The authors are to be congratulated for their efforts to educate the medical world about computing. In particular, the sections dealing with the diverse applications of computers in medicine were well thought out and informative. However, these reviewers feel that the very existence of some of the material in the book is a critical indictment of the operating systems which have left a large portion of the

medical community fearful to integrate computers into their daily routines. Graphic interfaces and the use of intuitive data entry devices such as pointers and eventually voice command facilitate the integration of computing into clinical practice and deserve more emphasis in this book.

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Myocardial Ischemia and Perioperative Infarction

J. G. Reves, ed. Anesthesiology Clinics of North America. Philadelphia: W.B. Saunders Co., 1988, 193 pp, $27.00.

Dr. Reves indicates in the preface that this book is aimed toward "the reader who in a busy practice must care for many patients with ischemic heart disease." The 200-page book is divided into nine chapters all oriented toward different aspects of ischemic heart disease. The quality of the chapters vary widely but all are written by individuals well versed in their fields. Each chapter is authoritative as well as current in thinking.

This reviewer especially enjoyed the chapter by Paul Wolff, MD, and Michael Nugent, MD, "Mechanisms of Myocardial Ischemia and Infarction." It provided a clear, basic description of the determinants of myocardial ischemia and the importance of these determinants in various disease processes. The chapter by Fiona Clements and Norbert de Bruijn entitled "Detection of Myocardial Ischemia and Infarction" was also an excellent, simple description of the major advances in monitoring (i.e., two-dimensional echocardiography, automated ST-segment analysis, etc.) that will be increasingly utilized for evaluating perioperative ischemia. In contrast, some chapters seem to be primarily literature reviews with short critiques of one study after another in rapid fire succession, each having major differences in experimental design and conclusions. Given the newness of much of the information and occasionally the controversy surrounding the subject, this literature review style approach does lend an impartial air to the material. For the cardiac anesthesiologist dealing with these problems on a daily basis, this approach is illuminating and interesting. However, for the occasional practitioner of cardiac anesthesia, this approach is both confusing and frustrating since the inevitable conclusion is that more research needs to be carried out before a definitive conclusion can be made.

Another criticism is that a topic may be covered multiple times in different chapters. For instance, four of the nine chapters have a section dealing with silent myocardial ischemia and two chapters deal extensively with the same myocardial pharmacologic agents. Though this redundancy was initially irritating, each chapter author does bring a different approach to the topic and provides additional information. In addition, for the busy practitioner looking

for immediate information, each chapter is essentially all-inclusive.

Despite the shortness of this volume, it serves as an authoritative, well-referenced, concise, up-to-date review of current thinking on a number of aspects concerning patients with myocardial ischemia. However, the volume is likely to be of more value to the practitioner who encounters the ischemic heart patient frequently rather than the occasional practitioner.

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Note: Price for annual subscription (four issues) of *Anesthesiology Clinics* is $65.

Capnography in Clinical Practice

J. S. Gravenstein, D. A. Paulus, and T. J. Hayes. Stoneham, MA: Butterworths, 1988, 158 pp, $21.95.

Capnography, a graphic display of airway carbon dioxide concentration, can prevent anesthetic disasters such as unrecognized esophageal intubation and airway disconnection. Gravenstein, Paulus, and Hayes show that when properly interpreted, capnograms can yield much additional information. Part I, "Clinical Perspectives on Capnography," describes the "anatomy" of a normal capnogram, the associated physiology, and the functional difference between mainstream analyzers (whose analyzing cuvette is part of the airway) and sidestream analyzers (which aspirate gas from the airway for remote analysis). Based on this background, the authors proceed to discuss factors which may affect the appearance of the CO_2 waveform. For example, changes in ventilation or CO_2 production may cause abnormally high or low end-expiratory CO_2 tensions. A gradually upsloping alveolar plateau suggests uneven alveolar emptying, while "dips" in the alveolar plateau may be the first indication that a mechanically ventilated patient is attempting to breathe spontaneously. Equipment malfunctions may also be distinguished by their characteristic capnograms: the presence of CO_2 throughout inspiration indicates a malfunctioning expiratory valve or exhausted sodalime. Experimental capnograms from Dr. Gravenstein's laboratory illustrate the CO_2 waveforms associated with Mapleson or Bain partial rebreathing systems. Unfortunately, the mechanism of cardiogenic oscillations in capnograms from mainstream analyzers is presented inaccurately: in fact, as with sidestream analysis, these oscillations result from reciprocal motion of the interface between end-tidal and fresh gas across the sampling site. With mainstream analysis, this interface is drawn toward the analyzer cuvette by the bulk flow of gas into the airway during apnea (apneic oxygenation). Part I concludes with a brief summary of clinical indications for capnography: detection of esophageal intubation or inadequate ventilation (e.g., ventilator disconnection), early diagnosis

of malignant hyperthermia, and adjustment of CO_2 tension in patients with intracranial pathology.

Part II, "Physiologic Perspectives on Carbon Dioxide," is a discussion of carbon dioxide production, transport, and elimination. The material is similar to that found in elementary physiology textbooks; however, errors in the text make parts of the discussion difficult to follow. For instance, the chloride shift is described backwards: the authors incorrectly state that when red blood cells buffer CO_2, there is "displacement of the chloride ion from the cell to the plasma . . ." (p. 67). Also, the authors use the partial pressure of oxygen rather than oxygen content in the calculation of shunt (p. 85). Because of such inaccuracies, Part II of the text should be skipped by those who are not familiar enough with the topic to recognize the errors.

Part III, Technical Perspectives on Capnography," is a discussion of the technical aspects of CO_2 analysis. After a discussion of general principles applicable to all methods of analysis (accuracy, calibration, response time, interference), separate chapters discuss each of the three available CO_2 measurement systems: infrared, mass spectrometry, and Raman scattering. The thorough, clearly-written discussion of infrared CO_2 analysis includes a description of filtering techniques (to reduce interference from gases with similar infrared absorption spectra); there is also a lucid introduction to the "pressure broadening" effect: diluent gases such as N_2 or N_2O may absorb energy from excited CO_2 molecules, allowing further infrared absorption and artifactually increasing the CO_2 measurement. The description of Raman scattering is similarly complete, and provides useful insight into this new technique of respiratory gas analysis. After deriving the basic mass spectrometry equation, the authors discuss its application to both fixed sector and quadrapole analyzers. The discussion of gas flow characteristics in different parts of mass spectrometer systems is excessive and inconclusive: summing networks built into the analyzer compensate for any errors which might be introduced by flow variations. However, these circuits may introduce errors if unanalyzed gases (e.g., aerosol propellants, helium) are present: these effects are clearly described in a separate section. Users of multiplexed mass spectrometer systems will benefit from the discussion of dwell time and breath detection algorithms. The final chapter returns to the issue of mainstream versus sidestream gas sampling; differences regarding such factors as airway adaptors, time delay, water condensation, and infection control are described in detail. Although one of the authors (Hayes) is employed by a manufacturer of mainstream analyzers (Hewlett-Packard), the discussion does not appear to be biased in favor of mainstream CO_2 analysis.

In conclusion, *Capnography in Clinical Practice* is a useful reference for those who wish to glean as much information as possible from the capnograms they observe in clinical practice. It also serves as a useful primer on the principles of CO_2 analysis. However, this book should not be used as an introduction to the physiology of carbon dioxide because of the errors in that section of the text.

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Acupuncture, Textbook and Atlas

Gabriel Stux, Bruce Pomeranz, eds. New York: Springer-Verlag, Inc., 1988, 342 pp, $69.00.

This book is a compilation of material from different books which the first author, Gabriel Stux, published earlier in German. It is intended for Western acupuncturists. An attempt is made to convince the reader of the validity of medical benefit of acupuncture by providing scientific data with the help of the second author, Bruce Pomeranz, a well-known researcher in acupuncture.

The book contains 15 chapters, an appendix section, and literature citations at the end of the book. The chapters do not have references except for the chapter entitled "Scientific Basis for Acupuncture." The first chapter provides evidence for scientific basis of acupuncture, and deals with the relationship of acupuncture analgesia to pain, drug addiction, and systemic diseases. This chapter is well written and provides good evidence for neural mechanisms of acupuncture analgesia, a strong relationship with endorphins and acupuncture and a possible synergism of serotonin and norepinephrine. The references provided in this chapter are up-to-date.

Chapters 2 and 3 cover history of acupuncture and a background on traditional Chinese medicine. It covers such topics as Yin and Yang, the cosmic vital energy: Qi, Shen on psychic energy along with internal emotional and external climatic factors. The chapter on history is only $1\frac{1}{4}$ pages long. The reviewer finds this inadequate. One would expect a more detailed account of history of acupuncture which is colorful, in a text book such as this.

Chapter 5 describes the Chinese system of channels, organs, and point. This is well written and makes it easier to understand what is considered otherwise to be a very difficult language. The illustrations are superb and clear and go a long way in allowing even a novice to understand acupuncture. The systematic description of channels and point occupies approximately 145 pages—about half of the whole book. Since this is a source book on acupuncture, this much space allocated to anatomic description of channels and point is appropriate.

Chapters 8–14 cover the techniques and all native methods of acupuncture with concise descriptions of acupuncture needles, electroacupuncture, moxibustion, laser acupuncture, acupressure, ear acupuncture, and hand acupuncture. For a novice who does not practice acupuncture, these chapters are useful, but for an acupuncture specialist, it is too superficial and elementary.

Chapter 15 provides a brief description for rationale for acupuncture treatment, rules of point selection, and selec-

tion of point for analgesic, sedative, tonifying, immune-enhancing, or homeostatic effect. The larger portion of the chapter deals with indication for acupuncture and selection of point for various medical diseases. To the anesthesiologist, this is not useful.

The appendices are somewhat useful but not all that necessary. For instance, Appendix G provides illustrations from The Golden Mirror of Medicine, a book published in the Quianlong era (1736–1796). This could have been easily incorporated into Chapter 2, which is a very short one indeed.

Overall, the book provides useful information on basics of acupuncture. This is of help to the novice acupuncturists. From the anesthesiologist's point of view, however, a lot of information is redundant since it is devoted to treating medical illnesses. The reviewer does recommend the book for one's personal library.

Basics of Acupuncture

Gabriel Stux and Bruce Pomeranz. New York: Springer-Verlag, Inc., 1988, 272 pp, $19.50.

The authors abstracted most of the information from *Acupuncture, Textbook and Atlas* and created another book. The book does not lose quality in its abstraction and maintains the information provided in the Textbook of Acupuncture.

It is less expensive and hence available to larger readership. The reviewer recommends it to the novice acupuncturist.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Abram SE. Cancer Pain. Current Management of Pain Series. Boston: Kluwer Academic Publishers, 1989, 173 pp, $69.95.

Davenport HT. Anaesthesia for the Aged Patient. Boston: Blackwell Scientific Publications, 1988, 328 pp, $65.00.

Roth BL, Nielsen TB, McKee AE. Molecular and Cellular Mechanisms of Septic Shock, Vol 286 in Progress in Clinical and Biological Research. New York: Alan R. Liss, Inc., 1989, 316 pp, $58.00.

Snow J. On Chloroform and Other Anesthetics, Their Action & Administration. Originally published in 1858 in London; 3rd reprinting. Park Ridge, IL: Wood Library Museum of Anesthesiology, 1989, 443 pp, $37.50.

Stanley TH, Sperry RJ, eds. Anesthesia and the Lung. Boston: Kluwer Academic Publishers, 1989, 301 pp, $84.00.

Zorab JMS, ed. Surgery for Anesthetists. Boston: Blackwell Scientific Publications, 1988, 512 pp, $165.00.

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Rovenstine EA: Combining anesthetic and surgical records for statistical purposes. Anesthesia and Analgesia: 1934; 13: 122–8 [185]

Seymour E: American Association of Anesthetists. Anesthesia and Analgesia: 1932; 2: 168–72 [332]

Thompson KW: Fatalities from spinal anesthesia. Anesthesia and Analgesia: 1934; 13: 75–9 [613]

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CHAIRMAN—DEPARTMENT OF ANESTHESIOLOGY
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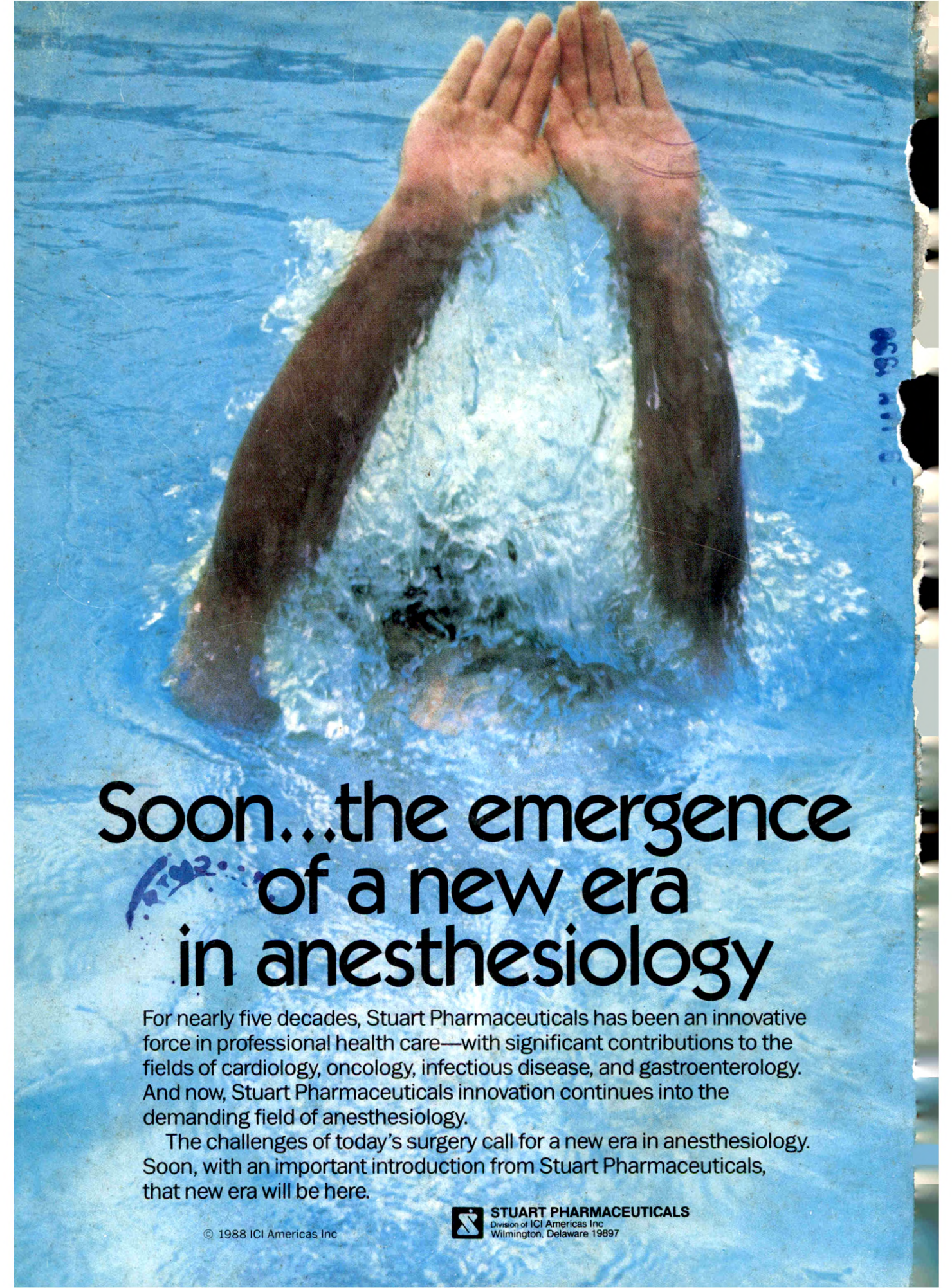
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